Applying a Person-Centered Approach to Enhance Cognitive Training in Senior Living Community Residents with Mild Cognitive Impairment (CogT-PACT study)

Study Protocol

NCT03292705

Date: 2/26/2018

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1. STUDY OVERVIEW – PURPOSE AND BACKGROUND

Computerized cognitive interventions (CCIs) have been increasingly widely implemented among older adults with mild cognitive impairment (MCI) (Jean, Bergeron, Thivierge, & Simard). Compared to traditional cognitive interventions, CCIs offer additional benefits including matching training content and difficulty with individual performance, visual appeal and variety, transportability, and scalability. However, the efficacy of CCIs in maintaining or improving older adults' cognitive and functional health has been modest in an overall sense, and highly variable across individuals and studies. For example, in a recently completed RCT in older adults with MCI, we found similar to others (Rebok et al., 2014; Wolinsky, Vander Weg, Howren, Jones, & Dotson, 2013) that vision-based speed of processing (VSOP) training, a widely-applied CCI, was superior to an active control in improving both trained (i.e., attention and processing speed) and untrained (i.e., working memory and instrumental activities of daily living) outcomes (Lin et al., in press). However, considerable variability appeared around the main effects for the intervention. This variability was not explained by typical demographic or clinical factors, leading us to suspect other processes at play in older adults' treatment response (Steinerman, 2011). Intriguingly, individuals' attitudes toward technology use may help explain the variety in VSOP training effects (Lin et al., in press). Negative attitudes about computers—defined broadly by affective, cognitive, and behavioral-motivational components, may interfere with engagement with, and thus the efficacy of, CCIs (Steinerman, 2011). Negative attitudes toward computers may be even more common in older adults with MCI (Wild et al., 2012), underscoring the crucial need to address them if CCIs are to achieve their full potential. The goal of this R21 application is to generate proof of concept for a means to address negative attitudes towards computer technology. Importantly, we will then assess whether improved attitudes toward computers enhance engagement with and efficacy of CCIs in older adults with MCI.

Person-centered care—that is, integrating individuals' preferences throughout the process of intervention--has improved intervention engagement among older persons, including those with MCI (Kolanowski, Litaker, Buettner, Moeller, & Costa, 2011). A recent intervention predicated on this person-centered approach is called a "personalized engagement program" (PEP). PEP involves a database of individualized computer-led leisure activities. Our recent pilot data in assisted living facilities suggest that PEP promotes psychological well-being among older persons with MCI, and may shift computers from dauntingly complex or personally irrelevant devices to familiar, enjoyable technology. These results are consistent with a number of theories indicating that exposure to pleasurable experiences with an object or task improves several dimensions of attitudes, including affective and cognitive components, as well as behavior and motivation. Theories of attitude change and motivation (Cervone, Artistico, Berry, & Hoare, 2006; Harmon- Jones, Amodio, & Harmon-Jones, 2009) suggests that PEP may act as a "mastery experience", pairing positive affect or better attention with successful goal-attainment in computer use, thereby reducing negative attitudes and increasing computer self-efficacy. If effective, this strategy would be the first to augment traditional CCIs with a non-cognitive psychological component (Lagana, Oliver, Ainsworth, & Edwards, 2011; Wild et al., 2012).

Grounded in both our pilot data and the theory around it, we seek to take the next step in an arc of research ultimately intended to improve the efficacy of CCIs. **Our Aim in this proposal is to conduct a small "proof-of-concept" randomized controlled trial (RCT) to assess whether an initial period**

of PEP, followed by a standard CCI, improves a) attitudes toward computers, b) affective and attentional engagement with the CCI, and c) cognitive outcomes, compared to an attention control period followed by CCI. Our design involving stratified random assignment of 50 senior living community residents with MCI from several similar senior living communities to these two groups. The initial phase involves 4 weeks of either attention control or PEP, a "dose" suggested by prior work on attitude change and computers, followed by 6 weeks of CCI for both groups (a period our prior work indicates is sufficient for change in key cognitive domains among this population). We will assess the following outcomes: (1) attitudes toward computers at baseline, 4 week, post-training, and a 3-month follow-up, (2) affective and attentional engagement in CCI during intervention period, and (3) multiple cognitive domains at baseline, 4 week, post-training, and 3-month follow-up. Since the interventions will occur in the senior living communities (SLCs), our design eliminates the burden of special visits to study locations and seamlessly integrates the intervention into daily routines. Equally as importantly, assisted living facility residents with MCI are at higher risk for developing dementias (Hyde, Perez, & Forester, 2007; Kaufer et al., 2008) and a high priority in NIA's mission to prevent Alzheimer's disease (e.g., PA-15-015). We thus feel that the study's impact upon the rapidly developing field of CCIs is potentially high, and ideal for the "high-risk high-reward" or proof-of-concept spirit of the exploratory, developmental R21 mechanism. Support for study hypotheses would form the foundation for a subsequent R01 taking the approach to full scale.

2. CHARACTERISTICS OF THE RESEARCH POPULATION

2.1. Subject Characteristics

a) **Number of Subjects:** A single-blinded, multi-site, randomized controlled trial will be conducted. A total of 50 participants will be recruited from several similar SLCs in the New York State. Randomization will be stratified by size of SLC (11 participants randomized to 2 groups in SLCs with 60-80 beds, 14 in SLCs with >100 beds).

b) **Gender and Age of Subjects:** aged 60 years or older. \ Most of the literature reports an equal gender representation in MCI population (although one or two regional studies reported higher incident rate of MCI in males from the Mayo Clinic). However, the proportion of female is significantly higher among SLCs (> 65%). We thus expect our sample to represent a balance between typical SLC composition and MCI distribution, and expect roughly 1/3 to 1/2 men (n = 17-25) and 1/2 to 2/3 women (n = 25-33).

c) **Racial and Ethnic Origin:** We plan to recruit 8% of minority (4 African American participants) from the SLCs. The percentage is higher than the 4% minority population in the Monroe County.

d) **Vulnerable Subjects:** All subjects will have the capacity to provide consent by assessing their comprehension and capacity of decision making.

2.2. Inclusion and Exclusion Criteria

a) **Inclusion Criteria:** (1) in-screening results which fall within the cutoff range of scores seen in 'mild cognitive impairment'
   i. $18 \leq \text{MoCA} \leq 26$
   ii. RAVLT Delayed Recall Total Score ≤ 6 (or 1.5 SD below age-corrected

norms)
iii. GDS Total Score ≤ 6
iv. ADL-PI-self Total Score ≤ 30
v. UBACC an intact score (score 2 on items 1, 2, 4, 7, & 9)
vi. if on AD medication (i.e., Memantine or cholinesterase inhibitors), antidepressant, or anxiolytics, no changes of doses in the 3 months prior to recruitment;
vii. others: age ≥60 years, English-speaking, adequate visual and hearing acuity for testing, resident of senior living community.

b. A board-certified geriatric psychiatrist (Dr. Porsteinsson, co-I) will review individual cases to ensure the validity of the MCI diagnosis (amnestic single- or multiple-domain phenotypes);

b) **Exclusion Criteria:** (1) current enrollment in another cognitive improvement study; (2) uncontrollable major depression: or other psychopathology identified by staff or medical records; (3) having active legal guardian (indicating impaired capacity for decision making); (4) medical history of AD or other types of dementia; (5) Not a resident of a collaborating senior living community

Eligibility will be determined after the screenings.

3. SUBJECT IDENTIFICATION, RECRUITMENT AND CONSENT

3.1. Method Of Subject Identification And Recruitment

Each SLC provides case management, at least one meal a day, housekeeping services, social and recreational activities. Randomization will be stratified by size of SLC (11 participants randomized to 2 groups in SLCs with 60-80 beds, 14 in SLCs with >100 beds). Staff at the SLCs will briefly introduce the study to the residents using the flyer. Residents who are interested in screening and learning more about study can leave their info on the flyer and the staff there will collect the information for the research team. The flyer includes a brief description of the study and space for individuals to leave their name, phone number, and e-mail address. SLC staff will secure the collected flyers in a locked cabinet in their management office specifically for the study purpose. Our research team will gather those periodically. Screening will be conducted at SLCs by our research team independently to avoid any potential perceptions of coercion by facility staff.

3.1.1. This study has also been registered on clinicaltrials.gov (NCT 03292705).

3.2. Process of Consent

After the initial phone screening process to determine interest and eligibility, any possible participants who wish to continue with an in-person screening assessment will be asked for their verbal consent to participate in the in-person screening. If verbal consent is provided, the interviewer will sign and date the verbal consent form and schedule the in-person screening appointment. An appointment letter can be mailed or e-mailed to the subject, if they wish, to confirm the appointment day and time.

At the end of the in-person screening stage, our research team will go over the main study consent form. Each possible participants' decision-making capacity will be assessed using UCSD Brief Assessment of Capacity to Consent (UBACC), based on the information given to them about the main study consent, to ensure older adults who attend the proposed study have adequate capacity

for giving consent and making decision. Subjects will not sign the consent form at this time – it is merely meant as a measure of decision making capacity to ensure eligibility.

A copy of main study consent form will be provided to potential participants for further consideration. They can read through the information before their first study visit.

At the first study visit, our research team will again describe the nature of the study and its risks and benefits and answer any questions and complete all additional elements of an informed consent process. The information included in the informed consent document includes: (1) the objective of the project as it relates to the examination of an intervention that addresses cognitive capacity; (2) description of timeline, the assessment and intervention procedure and components; (3) description of the environment where the assessments are conducted; (4) description of how the confidentiality regarding participant data will be protected; (5) description of the potential risk, relevant protections, and benefits of participating in the study. Each participant will sign the study-specific consent form. Participants are asked to answer five questions that assess their comprehension and decisional capacity to participate in research (ability to understand, appreciate, reason, and express opinions). The five questions were developed by Resnick et al's that specifically addressed the informed consent process among cognitively impaired patients. They are (1) "what are two potential risks?" (2) "what is expected from you?" (3) "what if you don't want to continue?" (4) "what if you experience discomfort?" (5) "how is it decided who gets the study intervention?" The health project coordinator will determine whether the participant's responses are adequate based on the criteria provided in Resnick et al's work. Each participant will sign the study-specific consent form. **Note:** If a participant fails to answer all questions correctly, the health project coordinator will re-explain relevant parts in the consent form. Participants are required to answer all questions correctly to continue the study. In our previous feasibility study, all participants succeeded in answering these questions. Participants will be compensated up to $70 for all study sessions they complete. The amount of compensation is considered appropriate for the intense and complexity of the study procedure.

4. METHODS AND STUDY PROCEDURES

4.1. Study Procedures and Assessments

Procedure:

A single-blinded, multi-site, randomized controlled trial of PEP+CCI, vs. control + CCI is involved. For PEP+CCI group, PEP will be implemented for the first 4 weeks, and CCI for the following 6 weeks. For the control + CCI group, an inert control condition, consisting of nothing outside of the ordinary, will be implemented for the first 4 weeks, and CCI for 6 more weeks. While we considered active control conditions, a reviewer pointed out that they pose challenges here if they share any computer or leisure components. As PEP is a solitary activity with a computer rather than a human-based intervention like psychotherapy, there is no "attention" (beyond that of the computer) to control. Research assistants provide the same set of assessments in each arm of the trial. Finally, at the developmental phase of an intervention design, an inert control is a sound starting point against which to test the new intervention. If proof of concept is achieved at this phase, subsequent trials will examine other types of control conditions. We will assess outcomes at the following time points: (1) computer attitudes at baseline, 4 week (the end of implementing PEP in the treatment arm), post-CCI training, and a 3-month follow-up, (2) engagement in CCI during intervention period, and (3) multiple cognitive domains at baseline, post-training, and follow-up. Assessments will be conducted by our research team. Separate staff blind to group assignment will conduct post-training and follow-up assessments. All intervention and assessments will occur in private rooms in relevant SLCs.

Interventions:

CCI. VSOP training will use the INSIGHT online program (Posit Science), which includes five training paradigms (Eye for detail, Peripheral challenge, Visual sweep, Double decision, Target tracker) that practice processing speed and attention. All exercises share visual components and focus on accuracy and fast reaction times. Participants respond either by identifying what object they see or where they see it on the screen. The training will automatically adjust the difficulty of each task based on the participant's performance, ensuring that the participants always operate near their optimal capacity. The training programs will automatically record the percentage of completion of each game and scores.

PEP. The PEP system is built on a picture-based touch-screen interface on tablet computers. PEP allows users to explore and participate in entertainment, educational, spiritual, and other recreational activities and content personalized according to their interests and preferences. It provides easy access to the Internet and communication applications, and has hundreds of modules spanning music, travel, trivia, games, and religious and inspirational domains. For instance, if music is among a person's lifelong interests, the PEP system provides access to multiple music genres through jukebox, karaoke and therapeutic music applications that can be tailored to a particular activity and by individual interest (for instance, a preference for classic jazz). As another example, for someone who likes travel or visiting new places, the interface offers access to Google Earth, guided tours, slide shows and regional facts and history. We will track the amount and type of particular usage (e.g., religion, travel, music, etc.) for each individual in the PEP+CCI group.

Intervention format and fidelity The PEP+CCI group will practice PEP for the first 4 weeks and VSOP for the following 6 weeks, and control + CCI group will receive attention control for the first 4 weeks, and VSOP for the following 6 weeks. Computer exposure interventions effecting attitude change have varied from a few days or a week [25,26] to 6 weeks[10]; we choose a median point as 4 weeks. The 6-week VSOP training duration is typical in the field, and similar to our prior work (Lin et al., in press). Orientations to PEP and VSOP will be provided using structured manuals developed from pilot studies and an on-going R01 VSOP project (see **Appendix** for training manuals). PEP will be individual based for 5 hours per week for 4 weeks, while VSOP will be delivered individually or based on small groups (3-5 persons), depending on a participant's preference, for 4 one-hour sessions per week for 6 weeks.. There will be sessions training and orienting the research team and staff of SLC on different aspects of the study.

Standardized fidelity assessments for both data collection and intervention modality will be used across multiple assisted living facilities. PI or project coordinator will observe a random 10% of the data collection and CCI sessions at each SLC. Competence (i.e., adhering to protocol measures and rules, consistency in administration, competency with measures and interpersonal skills with subject) will be assessed and feedback will be provided to individual assessors.

Measures:

Cognitive screening (T0): The cognitive screening battery will take approximately 30 minutes to complete. General cognitive functioning will be measured using the (a) Montreal Cognitive Assessment (MoCA) version 2, a common cognitive screening measure with high sensitivity to MCI and easily administrable. (b) The Rey Auditory Verbal Learning Test, lists C&D (RAVLT) is a measure of verbal learning and memory with high reliability and validity. Depression will be measured with the (c) Geriatric Depression Scale (GDS) – a series of yes or no questions concerning feelings of depression often seen in older adults. Subjective ability to perform everyday activities will be based on responses to all 15-items in the (d) Activities of Daily Living – Prevention Instrument (ADL-PI-self) questionnaire. Questions about demographic information, subjective memory complaints, family and

personal health history will also be asked during screening (K. Ball, Beard, Roenker, Miller, & Griggs, 2000; McGwin & Ball, 2002). Use of a cholinesterase inhibitor agent or Memantine and other medications and medical conditions will be confirmed after screening, with the subject's verbal permission, with their physician.

Attitudes toward technology use (Baseline [T1], End of Week 4 [T2], End of Week 10 [T3], & Week 23 [T4]): The Attitudes Towards Computers Questionnaire (ATCQ) will be used, one of the most common instruments assessing attitudes related to computer/internet. The ATCQ is a 35-item scale with 5-point Likert response options, assessing seven dimensions of attitudes toward computers: comfort (feelings of comfort with computers and their use); efficacy (feelings of competence with the computer); gender equality (the belief that computers are important to both men and women); control (the belief that people control computers); interest (the extent to which one is interested in learning about and using computers); dehumanization (the belief that computers are dehumanizing); and utility (the belief that computers are useful). It forms a single sum score, and can be broken down into subscale scores as well; our primary outcome is the former, although secondary analyses will examine the latter. The ATCQ has been used in prior research with elderly samples[25,26] including those MCI persons[53] with good internal consistency and test-retest reliability (both > .85) and validity. (Choi & Dinitto, 2013; Czaja et al., 2006; Czaja & Sharit, 1998)

Engagement in CCI (throughout VSOP training): The completion percentage and score of each of the five tasks in the VSOP training will be recorded automatically by the program by training session and as total. Training performance is calculated relative to the normative data in Posit Science database that have completed these same configurations and expressed as a percentile.

Cognitive and psychological measures (Assessment points: T1 -T4): The following assessments will take approximately 1.5 hours at each assessment period with breaks as needed, established durations acceptable for persons with MCI (Jack et al., 2008). a) Useful Field of View (UFOV) is a computerized test assessing visual processing speed and attention. This measure will not be administered at T2 to avoid practice effects (and we do not expect this measure to change after the engagement intervention).(K. K. Ball, Beard, Roenker, Miller, & Griggs, 1988; Deary, Johnson, & Starr, 2010; Melnick, Harrison, Park, Bennetto, & Tadin, 2013) b) EXAMINER, developed by the National Institute of Neurological Disorders, is a computerized test designed for clinical trials, measuring several executive function domains that are used to develop composite scores (verbal fluency, cognitive control and working memory). The test has been validated to detect cognitive function related to the prefrontal cortex (Possin et al., 2013). EXAMINER uses comparable assessment packages that are slightly different at each assessment point to avoid practice effects. For our purposes, only the following EXAMINER measures will be used to reduce subject burden while still assessing functioning: *Category Fluency*, *Flanker*, *Set-Shifting*, *Dot-Counting*, *1-Back*, and *Anti-Saccades*. c) Brief Visuospatial Memory Test (BVMT-R) is a well-validated battery of long-term visual memory in terms of learning and delayed recall, which also includes alternate versions of the test to avoid practice effects. To reduce subject burden, the optional copy trial of this measure will not be used. (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). These measures are commonly used and reliable and valid for patients with MCI, (Lin, Vance, Gleason, & Heidrich, 2012) and used in our previous work. d) Everyday Problems for Cognitive Challenged Elderly Test (EPCCE) is a variation of the well-validated Everyday Problems Test which uses printed information to measure the degree of functioning in instrumental activities of daily living in older adults with some degree of cognitive impairment. The EPCCE is made up of 32 open-ended questions (scored binomially & summed for total score or percentage correct) about 16 printed stimuli cards involving seven instrumental living domains (finances, medications, phone, shopping, transportation, household, and meals/nutrition), with high test-retest reliability (r = .94) (Willis, 1993) As each activity domain of the EPCCE is assessed twice throughout the measure, the test will be split into two versions (v1 & v2, used at alternating time points) with each domain being measured once in each version. This will be done to reduce subject burden and practice effects. e) Activities of Daily

Living – Prevention Instrument (ADL-PI-self) is a 15-item self-report questionnaire measuring overall functional ability over the past 3 months on a four-point Likert scale (from 1 – 4), where responses to each item are summed for a total performance score (higher scores indicate more impaired functioning) (Galasko et al., 2006). As the scale refers to functioning in the last 3 months, it will only be administered at screening, and T3 and T4. f) UCLA Loneliness Scale is a 20-item self-report measure of perceived feelings of social isolation and loneliness on a four-point Likert scale (from 1-4) resulting in a total score (higher scores for this measure indicate more feelings of loneliness and isolation, both of which relate to depression)(Russel, 1996). We will also note any medication or other health changes which occur during the trial.

Additonal information (Assessment point: Baseline): Self-report physical activities during the last year will be recorded with responses to the Victoria Longitudinal Study Leisure Activity Questionnaire (VLS) physical activity sections, and corroborated with SLC staff who observe the residents on a daily basis. To assess expectancy of change in attitudes toward computers, all participants will complete a set of items asking "How much do you expect your X to change in the next 4 weeks?" where X is one of the seven components of the ATCQ, and the response scale is a five-point Likert ranging from "Not at all" to "Quite a bit". At the suggestion of a reviewer, a four additional constructs known be associated with cognitive function will also be assessed by questionnaire: the Perceived Stress Scale (PSS),(Cohen, Kamarck, & Mermelstein, 1983) the NEO-Five Factor Inventory (NEO-FFI),(Costa & MacCrae, 1992) the Life Orientation Test (LOT),(Scheier, Carver, & Bridges, 1994) and the General Self-Efficacy scale (GSES)(Schwarzer & Jerusalem, 2010). These questionnaires as a set average about 25 minutes. They will be used in tertiary, exploratory moderator analysis intended to generate future hypotheses (rather than test current ones) about who might benefit most and least from PEPs. Future studies can then tailor or target PEP if indicated, to enhance its possible impact. The goal is not a formal qualitative analysis of these hypotheses, but rather to allow for the emergence of information that might "slip through the cracks" of questionnaires and which could be useful in refining the intervention in subsequent phases.

Outcome Measures	**Assesses**	**Time-point Used**
ATCQ Total Score	Attitudes towards technology	T1-T4
Engagement in CCI (% complete)	Engagement with VSOP intervention	During phase 2
EXAMINER (Forms A-C)	Executive functioning (cognition)	T1 (Form A), T2 (Form B), T3 (Form C), T4 (Form A)
UFOV	Visual speed of processing	T1, T3, T4
BVMT-R (Forms 1-4)	Visuospatial memory	T1 (Form 1), T2 (Form 2), T3 (Form 3), T4 (Form 4)
EPCCE (Versions 1 & 2)	Functioning in instrumental daily living activities	T1 (V1), T2 (V2), T3 (V1), T4 (V2)
ADL-PI-self	Self-perceived functioning in daily living activities	T0, T3, -T4
UCLA Loneliness 3	Self-perceived feelings of loneliness	T1-T4
Background/Tertiary Outcomes	**Assesses**	**Time-point Used**
VLS Physical Activity	Physical activity	T1
ATCQ Beliefs	Expected changes in attitude towards technology	T1
PSS	Self-perceived level of stress	T1
Neo-FFI	'Big 5' personality traits	T1

LOT	Optimism vs. pessimism	T1
GSES	Perceived self-efficacy	T1
Medication/Health update	Medication/health changes	T1-T4
Screening Measures	**Assesses**	**Time-point Used**
MoCA (v2)	General cognitive ability	T0
RAVLT (Lists C&D)	Verbal memory & learning	T0
GDS	Current depressive symptoms	T0
ADL-PI-self	Self-perceived functioning in daily living activities	T0
Demographic & health history	Anamneses	T0
UBACC	Capacity to consent	T0

As the living communities working with us on this study have other activities or research studies their residents participate in, we will also ask about whether they have participated in any other kind of cognitive intervention at 10 and 23 week follow-up appointments. This will allow to control for any confounding effects from other intervention programs or mentally stimulating activities in our later analysis. In addition, at the end of the study, we will send out a summary letter to all participants, will provide a summary of overall findings from the study.

4.2. Payment for Participation

Participants will be paid $20 at baseline, $10 at week 4 intermediate assessment, $20 at week 10 post training assessment, and $20 at week 23 follow-up. Together, participants will be paid $70. If a participant does not complete all sessions, he/she will be paid for the completed portion. The entire study procedure will occur in relevant SLCs, so no need for transportation.

4.3. Return of Individual Research Results

For newly diagnosed MCI, we will emphasize the screening is for research purpose, not a clinical diagnosis. We will suggest the participant schedule an appointment with their PCP or the clinician taking charge of relevant SLC to discuss the test results, and we will also refer the participant to the local memory clinics if the participant prefers. We will send a final summary of the study findings assembling de-identified information from all participants.

5. SUBJECT WITHDRAWALS

Participants will be advised during the consent process and the actual study process that they have the right to withdraw from the study at any time without prejudice.

6. RISK/BENEFIT ASSESSMENT

Risks to participants for this study are expected to be minimal.

6.1. Risks to Subjects

Some assessments carry the potential risk of being perceived as burdensome by some participants, although no sustained negative effects from assessments are expected.

Although the assessments involved in the study have been regularly used in clinical diagnosis, the challenges and potential failures from completing the assessments may produce frustration to the participants.

Participants will be instructed that they can take a break or discontinue the assessment or training at any time during the assessment or training session.

The alternative to PEP+CCI intervention is to participate in a CCI alone intervention, which has been demonstrated to improve a broad range of cognitive functions in patients with MCI. All participants will be reminded of the voluntary nature of study participation.

Concern about identification of depression and suicide intention during the screening via the research team: We exclude participants with major depressive disorder who have currently (<3 months ago) changed their dosage or type of antidepressant or anxiolytic medication, or have a total Geriatric Depression Scale score of 7 or higher (with scored between 5 and 6 to be further clarified by the clinicians), so as to avoid patients with unstable major depression or psychiatric disorders. We do not expect the PEP or CCI induce any depressive or anxious symptoms from the training. In fact, cognitive training programs have been constantly used to reduce psychiatric symptoms among older adults in previous studies. Also, we do not expect to observe any suicide intention from this group of participants. The literature does not suggest the diagnosis of MCI is attributed to the likelihood of suicide. Regardless, one of the co-Is, Dr. Porsteinsson is a board certified geriatric psychiatrist. He will provide immediate care to any participants at risk of suicide or clinically unstable. If a participant is judged to be at immediate high risk and leaves study venue against the advice of Dr. Porsteinsson, we will contact the clinician taking charge of the relevant SLC.

Protection against risks: During informed consent procedures, individuals will be told about possible risks and benefits of participation. This will include questions or tests that may cause them to feel uncomfortable or upset. They will be informed that should they feel upset they should tell the interviewer, and he/she will provide a break. They will be informed that: they may withdraw from an assessment at any time for any reason and receive full reimbursement for that assessment; and, they may withdraw from the research study at any time without negative consequences. Of note, except providing a brief introduction of the study, the SLC staff will not be involved in the study procedure. Residents' direct health care provided by the SLC will not affected by their decision on participating in, or later, withdrawing from the study.

Psychological distress: Potential interviewers will be trained to detect distress and take immediate action to reduce the participant's distress. This may mean having the participant take a break, get something to eat, or finish for the day. The interviewer will be taught to intervene in a calm fashion and give the participant time to talk and become more relaxed. If these measures do not alleviate the problem, the interviewer will be instructed to contact the research team (Dr. Porsteinsson, a geriatric psychiatrist) for additional assistance. With the participant's permission, we will also contact the relevant staff and physician working at the SLC.

Ongoing monitoring of medical changes. We will monitor cognitive assessments across all assessment points. If we find any participant's assessments fall below the range of scores for MCI, we will notify their SLC staff and physician with permission for further follow up and clinical assessments.

Confidentiality and privacy: All hard-copy based materials and data will be kept in a locked research office in a locked file cabinet. No one other than the research team will have access to the data. The list of affiliated SLC address, and the study ID numbers associated participants' confidential information (i.e., names, gender, age, unique identification code in the affiliated SLC) will only be stored in study management software (e.g., Filemaker Pro) in a secure manner. In separate data management software (e.g., Excel, SPSS), there will only be the study ID number associated with individuals' responses to the questionnaires. All computer-based materials and data will be kept in password-protected server at School of Nursing. Servers at the School of Nursing are routinely audited for vulnerabilities or improper configurations by relevant Information Security team.

Note. In the two intervention platforms (PEP and VSOP), participants are asked to enter the ID they get assigned. Despite no private health information will be provided on the intervention platform, we will still address the protection of participants' activities in the platform, including: (1) in conjunction with the PI, the highly experienced IT staff will secure the intervention site and its operations; (2) the intervention platform, where individual training (both PEP and VSOP) data will be housed, will be accessed through secure password protected processes; (3) Online data from PEP and VSOP training will only be accessed by the participant and investigators and study staff directly involved in this study through secure password protected processes. The PEP and Posit Science which own the training programs, have constructed data transport and storage systems to be HIPAA and FIPS-140 compliant.

6.2. Benefits to Subjects

According to the Alzheimer's Association report, there are 5.4 million persons who have Alzheimer's disease (AD), whose care cost 200 billion dollars in 2012 and affected 10.9 million informal caregivers. To develop strategies that can prevent or slow the progression of AD is the highest priority of AD research. If the intervention is efficacious, and more importantly, if the underlying mechanism is fully understood, it will provide the basis for a larger, more definitive trial where its efficacy can be determined. Long term participants may benefit from an improvement in cognitive abilities. Given the risks to participants, and the scientific importance of the proposed investigation, the risk/benefit ratio is highly favorable and supports the ethical reasonableness. As will be noted in the consent form, some subjects may benefit from the interventions, but others may not have any direct benefit from study participation.

If the intervention is successful at improving cognitive abilities, then there may be a benefit to future patients. The study may also provide important information on the role of PEP+CCI training in contributing to health and well-being and the importance of suggesting a mentally active lifestyle in patient-health care provider interactions, further informing health practices.

6.3. Alternatives to Participation

All participants will be informed that their participation is voluntary. They can choose not to participate and they may withdraw from participation at any time without affecting their care. Also, participants will be informed that if they feel undue burden and/or become tired with participation that they may stop the interview at any time, reschedule, or withdraw from the study if desired. Participation in the study does not preclude participants from using resources that are usually available to patients with cognitive deficits.

7. CONFIDENTIALIATY OF DATA AND INFORMATION STORAGE

In School of Nursing (SON), we have a confidential data storage system called MIS system, which is protected by password and SON computer/internet security system per HIPPA regulation. Only members of the research team have access to the MIS system that is related to the study.

All screening information will be assigned a "Screening ID" once the permission to contact information is received and stored in locked drawer in study file. Information from the screening information will also be entered to the MIS system. In the MIS system, if a patient is screened and not eligible or not interested, then no identifying information (names, etc.) will be kept in MIS. The information from these forms will be used to monitor reasons for exclusion. If a patient is interested in enrolling – we keep name/address (for appointment letters) – and then assign ID after consented.

All patient data collected for research purposes will be obtained with the written consent of the patient. After written informed consent has been obtained, participants will be given an actual "ID number". Questionnaires and demographic information will be recorded only with ID numbers. This actual ID number will also be entered into the MIS system. All hardcopies of questionnaires and demographic information will be kept in a secure file in a research office at the School of Nursing and saved for seven years. At the completion of the subject's participation or coding of data the data would be de-identified to further protect the subject's privacy and confidentiality of the data. All of the data will be entered electronically by the PI or the data management team from the School of Nursing in the investigator's computer at the SON and saved as a back up to the University main server. All electronic data from questionnaire, biomarkers, and demographic information will be stored on the School of Nursing network drive, which is password and firewall protected per HIPPA regulation, so that the PI can oversee the process. Access will be given only to those persons directly involved with the research. Individual data will not be available to anyone outside the proposed research team without the written consent of a participant. Confidentiality will be assured by the maintenance of the data in locked offices at the School of Nursing and by restricted access to computerized data. Participants will be assured that all data will be reported without identifiers and reported in the aggregate.

The only place that link the "Screening ID" and "Actual ID" is the MIS system and the blue envelope utilized to randomize the participant (kept in the study file). We will use MIS system to contact participants for any follow-up contact (e.g., phone interview, schedule appointments).

8. RESEARCH INFORMATION IN MEDICAL RECORDS

N/A

9. DATA ANALYSIS AND DATA MONITORING

9.1. Planned Statistical Analysis

The general modeling strategy will implement Generalized Mixed Effects (GLMMs) models with random effects for subject and site. The latter (i.e., random effects), if non-significant given the small number and similarity of sites, can be dropped. GLMMs yield valid estimates if data are Missing at Random (i.e., predictable from observed covariates) and offer the flexibility to deal with any distribution of outcome within the exponential family. Most outcomes are likely to be normal, but appropriate links and distributions will be used as needed. Given the smaller sample size of the trial, rather than relying on large sample theory standard error estimates, we will use clustered bootstrap standard errors (Field & Welsh, 2007). **Power analyses.** Sample size estimates are based on effects in our (Lin et al., in press) and others' (Valdes, O'Connor, & Edwards, 2012; Wolinsky et al., 2013) previous work. Using a two-sided alpha = .05, this study has 80% power to detect medium effects (≥ 0.5) for the group effect on attitudes toward technology (H1), engagement in VSOP training (H2), and cognitive outcomes (H3). **Preliminary Analyses.** Distributions will be visually inspected for outliers, and determine the

best link and distribution combination for each outcome using the Quasi Information Criteria (Pan, 2001). The groups will be compared to determine systematic differences (failure of randomization) on potential covariates using Chi-square, T-tests or nonparametric analyses, as appropriate. Those found to significantly differ between groups will be included in models. For each hypothesized outcome (H1: attitudes toward computer use, H2: engagement in VSOP training, H3: 5 cognitive outcomes), model specification will include time, group, and their interaction as predictors (and controls as needed). Linear contrasts will test intervention effects at post-intervention. A separate model will also verify that ATCQ scores show significantly greater improvement at 4 weeks in the PEPs group as expected. Secondary analyses will examine the association between ATCQ scores at 4 weeks and CCI outcomes. ATCQ scores are intended to be systematically higher in the MCI+CCI group by design, but considering then on a continuous scale provides additional information about the "dose response" or slope of the association between attitudes and CCI improvements. Secondary analyses will also consider different domains of attitude change, explore gender moderation, and correlations between amount of attitude change and engagement/cognitive change. A set of tertiary, hypothesis-generating analyses for future intervention refinements will examine the optimism, stress, general self-efficacy, and the Big 5 as potential moderators. Finally, sensitivity analyses will employ multiple imputation to further probe the impact of any drop-out, and multiple comparisons will be conducted under False Discovery Rate control.

9.2. **Data and Safety Monitoring**

This is a pilot randomized controlled trial study (Phase I). The MPI (Dr. Lin and Dr. Chapman) will oversee the project, and hold regular monthly conference call with the research team, including SLC staff members. For each monthly meeting, the PIs will present an overall progress statement. The issues/concerns related to the safety of participants will include

(1) the evidence of safety issues that should be addressed;

(2) all serious adverse events, determine whether individual patients should be removed from the protocol. We acknowledge that there may be rare instances where some emergent situation occurs that was unanticipated regarding the welfare of the participant. In these situations, the UR IRB may be contacted to help resolve the situation.

In addition, the following steps will be taken to protect the confidentiality of data and computer records and participant safety:

1) Confidentiality will be assured by the maintenance of the data forms in locked offices, and by restricted access to computerized data. Only core research team members will have access to the name, address, telephone number, and other information corresponding to each identification number. Participants will be fully informed of the study requirements throughout the conduct of the study and will be allowed the opportunity to withdraw from participation if they cannot, or do not comply with the rigors of the research protocol. Handling of data will be limited to the numerical values and statistical summaries.

2) Identifiers linking identification codes with individual names will only be available to the PI and study staff who contacts participants.

3) The MPI have obtained the policies of the UR IRB specifically regarding adverse events associated with the study. The MPI will adhere to those policies, and maintain a copy of the policies in the study file.

4) The investigators will protect the health and safety of participants, inform them of information relevant to their continued participation (e.g., newsletters) and pursue the research objective with scientific diligence.

5) The following policies required by our IRB and NIH will be adhered to: (1) any adverse events that are serious and unexpected and are related (possibly or probably) to the study will be reported to the IRB and NIH within 15 calendar days; (2) adverse events that are both unexpected

and related that are either life threatening or result in death will be reported to IRB and NIH immediately; and (3) for adverse events that do not meet the criteria above will be documented in the summary report submitted to the IRB and NIH annually at the time of the study's continuing review. Because the proposed study is minimal risk, we do not anticipate any serious adverse effects as described in the first two categories from a result of participating in this study.

6) The MPI will ensure that the NIH (funding Institute and Center) is informed of actions, if any, taken by the IRB as a result of its continuing review, and recommendations that emanate from the monitoring activities.

7) The MPI will be responsible for monitoring of this plan throughout the life of this study.

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