Computerized Cognitive Training to Improve Cognition in Diabetic Elderly Veterans

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Principal Investigator/Study Chair: Jeremy Silverman, Ph.D.

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Abstract

Project Background: Diabetes mellitus (DM) has consistently been associated with increased risk for cognitive decline, mild cognitive impairment, and dementia in the elderly. Even minor cognitive impairments in nondemented individuals dramatically affect disease self-management. This, in turn, is associated with poor glycemic and blood pressure control in diabetes, which by themselves increase the risk of dementia, provoking a reinforcing cycle of disease. Thus, it is imperative to find interventions to delay or prevent cognitive compromise in diabetic patients, that can be relatively easily and rapidly implemented, and that are not cost prohibitive. This is especially true in the VA, in view of the high incidence of both diabetes and dementia in our growing population of elderly Veterans.

Epidemiologic evidence suggests modifiable life-style factors, including cognitive activity, may prevent or delay the onset of cognitive decline. Computerized cognitive training (CCT) is an intervention that has shown promising results in the improvement of cognitive functioning, more consistently in non-demented elderly, with additional benefits from booster training sessions. To date, studies of CCT have typically only examined cognitive outcomes, and only shortly after the intervention. The proposed CCT program, Personal Coach from Cognifit, is designed to improve cognition of elderly persons by targeting their weak cognitive functions, using a personally tailored training plan. The proposed study will provide the first evaluation of the effects of CCT on DM self-management behavior and clinical outcomes, in addition to cognition.

Project Objectives: Aim 1A: To determine whether the CCT, relative to the active control games program, improves cognition (memory and executive functions/attention), DM-related behavior (DM self-management and medication adherence), and clinical outcomes (glycemic and blood pressure control), 6 and 12 months after the intervention. **Aim 1B**: To demonstrate efficacy by improvement in behavioral outcomes (DM self-management and medication adherence) 6 months after the intervention. **Aim 2**: To document the effects of CCT on the successive changes in memory and executive functions/attention, DM self-management and medication adherence, and glycemic and blood pressure control. **Aim 3**: To explore the impact of demographic (age, education, ethnicity, site) and health (ADL/IADL, health literacy, depression, dementia family history, lifestyle factors) characteristics, on the intervention effects.

Project Methods: Non-demented DM elderly from the James J. Peters (Bronx, NY) and Ann Arbor (MI) VAMCs will be randomized to CCT or games intervention and perform the respective program 3 days per week (every other day), for 20 minutes, for 24 total sessions. Four months after the intervention, subjects will receive a 1-week booster training. Subjects will be assessed at baseline; and immediately, 6 months, and 12 months after the intervention. At each time point, assessments will be cognitive function, DM self-management, and blood pressure; blood will be drawn forHbA1c measurement. VA records will be used to monitor medication adherence. Longitudinal mixed model analyses will assess the effects of the intervention on change in outcomes overtime. Path analyses will evaluate the inter-relationships among changes in cognition, DM self-management, and clinical outcomes for each intervention at 6 and 12 months.

List of Abbreviations

Provide a list of all abbreviations used in the protocol and their associated meanings.

Activities of Daily Living/ Instrumental Activities of Daily Living (ADL/IADL
Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE)
Alzheimer‘s disease (AD)
Clinical Dementia Rating (CDR)
Computerized cognitive training (CCT)
Dementia Rating Scale (DRS)
Diabetes mellitus (DM)
Geriatrics Research, Education, and Clinical Center (GRECC)
James J. Peters VA Medical Center (JJP VA)
Mild cognitive impairment (MCI)
Mini Mental State Examination (MMSE)
Unified Data Set (UDS)
Wechsler Adult Intelligence Scale (WAIS)

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1.0 Study Personnel

Principal Investigator/Study Chair:
Jeremy Silverman, Ph.D., Professor, Mount Sinai School of Medicine and Research Scientist and Clinical Psychologist, James J. Peters VAMC, 718-584-9000 ext 1700, jeremy.silverman@va.gov and jeremy.silverman@mssm.edu

Co-Investigators:
Hillel Grossman, M.D., Team Leader Geriatric Psychiatrist, James J. Peters VA Medical Center, 718-584-9000 ext 5752, hillel.grossman@va.gov

Joan Penrod, Ph.D., Health Science Specialist, James J. Peters VA Medical Center, 718-584-9000 ext 3814, joan.penrod@va.gov

Mary Sano Ph.D., ACOS R&D, James J. Peters VA Medical Center, 718-584-9000 ext 6009, mary.sano@va.gov

James Schmeidler, Ph.D., Assistant Clinical Professor Psychiatry, Mount Sinai School of Medicine,212-659-8838, james.schmeidler@mssm.edu

Elizabeth Guerrero-Berroa, Assistant Professor, Icahn School of Medicine at Mount Sinai, 718-584-9000 x5182 elizabeth.guerrero-berroa@mssm.edu

Pearl Lee, MD., Physician Scientist, VA Ann Arbor Healthcare System, 734-769-7100, pearl.lee2@va.gov

Neil Alexander, M.D. Co-investigator, GRECC director, , VA Ann Arbor Healthcare System, 734-845-3048, vhacogreccwm@va.gov

Sarah Krein, PhD, RN, Research Scientist, VA Ann Arbor Healthcare System, 734-845-3502, sarah.krein@va.gov

Collaborator: (Consultant)
Michal Schnaider Beeri, Ph.D., Associate Professor, Mount Sinai School of Medicine, Director, Joseph Sagol Neuroscience Center, Sheba Medical Center, 212-659-8807, michal.beeri@mssm.edu

2.0 Introduction
BACKGROUND

Diabetes is a risk factor for dementia and cognitive decline. There are numerous studies demonstrating consistently higher risks of dementia, mild cognitive impairment (MCI), and cognitive decline in persons with diabetes. Diabetes or impaired fasting glucose may be present in up to 80% of persons with Alzheimer's disease (AD)[1]. This is a significant health concern not only for the general population, but also specifically for our Veterans since the incidence of dementia is as high or higher in elderly Veterans[2] as in the population at large and diabetes prevalence is also accelerating[3]. A systematic review of the effect of diabetes on dementia and cognitive decline concludes that cognitive impairment should be considered a consequence and disabling manifestation of diabetes[4], and the 2010 *NIH Consensus Development Conference Statement on Preventing Alzheimer's Disease and Cognitive Decline* listed diabetes first as a risk factor[4]. Thus, interventions to prevent cognitive impairment and dementia in diabetic elderly patients are imperative in order to halt this devastating epidemic that affects the patients, their families, and the society as a whole emotionally and financially. Furthermore, increased MCI and dementia have been associated even with pre-diabetes[5]. This is significant from a public health perspective, since it suggests that the mechanisms underlying the increased risk of cognitive compromise in diabetes may be generalizable to non-diabetic individuals. Thus, this study may shed light into potential therapies to prevent dementia in all elderly.

The current lack of disease-modifying treatment for Alzheimer's disease (AD), and the robust epidemiologic evidence suggesting modifiable protective life-style factors (eg. cognitive and physical activity[6]) have led to particular interest in life-style interventions that may delay the onset or slow the progression of cognitive decline. The Alzheimer's Association —Maintain Your Brain‖ campaign recommends staying mentally active as one of the key components of a —brain healthy lifestyle. In addition, the Alzheimer's Association has recently partnered with the Centers for Disease Control and Prevention to develop the —Healthy Brain Initiative‖, which recommends studying the effects of mental activity as part of its road map for maintaining or improving the cognitive performance of adults. The Institute for the Study of Aging chose to specifically promote neurogenesis—which is induced by cognitive enrichment—rather than treatment to address neuropathology, as a therapeutic strategy for cognitive aging and AD[7]. These recommendations are based on studies demonstrating that the brain is highly plastic and capable of generating new synaptic connections and neurons throughout life[8], particularly when activated by enriched environments. Enriched environments that target sensorimotor modalities[9] have been shown to improve cognitive function[10], facilitate recovery from injury or stroke[11], and prevent age-related decrease in synaptic density in the aged brain[12]. Such enriching environments have also been shown to increase brain weight[13], cortical thickness[14], [15], and neurotrophic factors[16]. Mice raised in an enriched environment—that includes access to mental activities such as colorful toys and tunnels—generate more neurons in the hippocampus[17], an area playing a central role in memory formation and severely affected in AD. These animals also experience reduced cerebral deposition of β-amyloid, a pathological hallmark of AD[18]. Moreover, neurogenesis has been reported also in the brains of old animals, both in the hippocampus[19] and in the forebrain[20]. In humans, several prospective longitudinal studies have shown that elderly who engage in more mental activity, such as reading or playing games, are less likely to develop dementia and AD.[21,22]

As described above, the presence of neurogenesis and neuroplasticity into old and even very old age is the underlying rationale for cognitive training as a therapeutic venue to enhance cognition. A variety of interventions, including mnemonic training, group learning sessions, individual piano instruction, audiotape memory training, and more recently computerized training, have been suggested to delay cognitive decline in non-demented elderly[23]. Cognitive

interventions have been shown relatively consistently to improve cognitive functioning in individuals with no cognitive impairment[24,25]. Results for cognitively impaired individuals are less consistent. For MCI two studies using global cognition as the outcome measure showed cautious but positive results[22, 26] while another study found that MCI subjects improved in reasoning and speed of processing but not in memory when trained in these respective functions[27]. Similarly, some studies have shown positive results for early AD[28], although a Cochrane review concluded that methodological limitations precluded a strong demonstration of efficacy[29]. These improvements are found both in general cognition and in specific cognitive domains[30-34], including attention, executive functioning, explicit memory, reasoning, speed of processing, and spatial orientation[35]. Of note, a recent investigation of the effects of a 6-month cognitive intervention program on brain metabolism in MCI and mild AD patients found that MCI patients had cognitive benefits from the training that were accompanied by attenuated decline of glucose metabolism in cortical regions affected by AD[36]. This pattern was not present in AD patients, suggesting that the cognitive and neuronal metabolism benefits derived from cognitive interventions are more effective before the dementing process has been broadly established. The Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, the largest randomized trial published so far, found that cognitive training results in cognitive improvements specifically for the trained cognitive function (e.g., memory)[37]. The ACTIVE study also found that cognitive training reduces functional decline in self-reported IADLs[33] as well as increases health-related quality of life[37]. Importantly, these improvements persisted five years after the initiation of the intervention. Similar to the ACTIVE trial, cognitive training has been shown to affect areas beyond cognition, such as increased quality of life perception[38], health-related quality of life[37], improved driving behavior[39], and improved gait[40]. In contrast to the ACTIVE trial, other studies have shown that training generalizes to cognitive functions beyond what was trained[37 (but see34)] and to have durable benefits[31]. These promising findings, in addition to the various advantages of nonpharmacological interventions (such as lack of physiological side-effects so common in the cholinesterase inhibitors), are a basis for the recent emphasis on cognitive activity and specifically cognitive training in the fight against cognitive decline and AD (see section B2). Computerized cognitive training (CCT) is currently one of the most commonly used forms of cognitive intervention. Although a concern of providing CCT to the elderly is the lack of familiarity with the technology, there has been a dramatic increase in the number of older adults buying and using computers[24], a trend that is accelerating. Census estimates of the US population 65+ years of age —having internet access in the household increased from 29.4% in 2001 to 45.7% in 2007 and then to 53.3% in 2009. The rates of —using the internet at any location similarly increased from 19.8% to 34.9% and then to 41.5%. CCT programs have the advantages of being multimedia and interactive, performed at the residence of the participant, having flexible hours of use, and being available for continued use after the intervention period ends. They also avoid the need for a live instructor throughout the training period reducing costs. Further, some CCT programs have the capability of adjusting the content or level of difficulty of the tasks to the user. For research contexts, every response by a participant is recorded and saved automatically, maximizing opportunities for assessing change while minimizing data entry mistakes and difficulties. The CCT proposed in this study, Personal Coach, improved both cognitive (visuospatial working memory) and non-cognitive outcomes (gait[30]) primarily when using CCT before the development of overt dementia, with —large effect sizes. Since diabetic patients are at particularly high risk for developing dementia, the proposed randomized trial will examine the immediate (2 months after initiation of training), short-term (8 months) and longer-term (14 months) effects of CCT in nondemented diabetic elderly Veterans.

In diabetes, medication adherence is typically considered a central component of disease self-management[44] because pharmacological therapy is a cornerstone of treatment, both for glycemic control and for managing cardiovascular risk factors such as blood pressure. Nonetheless, approximately 50% of diabetic patients are not adherent to diabetes medications[45,

[46]. Multiple factors influence poor medication adherence, which is associated with more severe disease progression, avoidable hospitalizations, disability, and death[47,48]. While the implications of dementia for medication adherence are obvious, even non-demented elderly individuals with the mildest cognitive impairment have increased risk for poor medication adherence. In a study of independently living healthy elders, those with lower cognitive scores had significantly worse adherence (measured using an electronic 7-day pillbox; relative risk of ≥20% of days non-adherent = 4.1)[49]. Similarly, executive functions and working memory were predictors of medication adherence in another study of community dwelling cognitively normal elderly50. Higher scores on verbal memory and executive functions were associated with successfully setting up a medication schedule and with medication adherence in another study of community dwelling elderly[51]. This supports our choice of memory and executive functions/attention as primary cognitive outcomes and suggests that CCT may enhance medication scheduling and adherence. Performance in cognitive function tests, among non-demented elderly referred to a geriatric assessment unit, was significantly poorer in those demonstrating lack of basic knowledge of their medication regimen[52]. More generally, cognitive performance predicts poor medication adherence in many contexts and diseases. In the Framingham study, among hypertensive subjects who had previously been prescribed medication, cognitive deficits were associated with reduced medication adherence[53]. Specifically, those in the lowest 10th percentile of education-adjusted cognitive performance were over three times as likely to have stopped treatment than those in the normal performance group. Non-adherence behavior after hospital discharge was examined in a sample of a general clinical population and poor memory was one of the significant predictors[54]. Cognitive deficits predicted poor medication adherence in patients taking anticoagulants[55] and in rheumatoid arthritis[56] and COPD[57] patients. In older patients with schizophrenia, cognitive functioning predicted medication adherence above and beyond age, gender, education level, symptom severity, and attitudes towards medication[58]. In a review of treatment adherence studies in older patients with Parkinson‘s disease it was concluded that —neuroprotective regimens may give rise to better adherence[59]. Cognitively impaired patients are more likely to have poorly controlled blood pressure due non-adherence[60]. Diabetic patients have higher prevalence of white matter hyperintensities[61], which have been associated with poor medication adherence[62] suggesting an underlying biological substrate for low medication adherence in diabetes. Thus, healthy cognition is a critical factor for successful medication adherence in other diseases, as well as diabetes. The literature on general self-management in diabetes is more limited, but the relationships with cognition are in the same direction as for medication adherence. Cognitive impairment (Mini Mental State Exam<23) was associated with poor diabetes self-management (eye, foot, and dietician assessments) in diabetic elderly subjects above the age of 75[63]. Similarly in a population-based study of 1398 diabetic patients aged 55 and older, subjects with mild and moderate cognitive impairment (based on the Telephone Interview for Cognitive Status) were significantly less adherent to exercise and to diet[64]. These studies provide evidence for 1) diabetic patients having high non-adherence to medications; 2) cognitive functioning, and specifically memory and executive functions, being associated with self-management and medication adherence; and 3) this relationship occurring even with the mildest cognitive dysfunction and consistently across several diseases and conditions. Thus, they support this investigation of the effects of CCT on medication adherence and self-reported diabetes self-management, in a sample of non-demented diabetic elderly Veterans. They also support the examination of the clinical manifestations, glycemic and blood pressure control.

In the absence of CCT, diabetes increases risk for cognitive compromise, which increases the risk for poor medication adherence and other disease self-management behaviors, which in turn increases poor glycemic and blood pressure control, increasing the risk for cognitive compromise[65], and thus developing a reinforcing cycle of disease ultimately resulting in increased diabetes complications, hospitalizations, and death. The model implies

that improvement in cognition, due to CCT, impedes formation of this cycle, by counteracting the cognitive compromise that initiates the cycle. Aim 1 examines the effects of CCT on cognitive, behavioral, and clinical outcomes, in diabetic elderly. Aim 2 goes beyond assessment of efficacy to validate the linkages among these outcomes in the conceptual model, by evaluating the associations through which CCT affects the successive cognitive, behavioral, and clinical changes.

3.0 Objectives

Diabetes mellitus (DM) has consistently been associated with increased risk for cognitive decline, mild cognitive impairment (MCI), and dementia. Our prior research shows that 1) subjects with diabetes in midlife had a 3-fold increased risk of dementia three decades later, 2) diabetic elderly with the earliest signs of cognitive compromise have a faster rate of cognitive decline, 3) glycemic control is associated with cognitive decline even in non-diabetic individuals, and 4) diabetes medications are associated with fewer neuritic plaques, a hallmark Alzheimer‘s disease (AD) neuropathological feature. Additionally, numerous studies have shown that in non-demented individuals, even minor cognitive impairments dramatically affect their adherence to medications and disease self-management in general. Those in turn, are associated with poor glycemic and blood pressure control in diabetes, which by themselves increase the risk of dementia, provoking a reinforcing cycle of disease. Importantly, there is evidence indicating that the brain itself regulates systemic glycemic control. Thus, it is imperative to find interventions for diabetic patients that prevent impaired self-management by maintaining a healthy brain, and that can be relatively easily, rapidly, and cost-effectively implemented. This is especially true in the VA, given the high incidence of both diabetes and dementia in our ever growing population of elderly veterans in treatment. The current lack of disease-modifying treatment for AD and dementia, and epidemiologic evidence suggesting modifiable protective life-style factors (e.g. cognitive activity), have provoked investigations of lifestyle interventions to delay the onset of or to prevent cognitive decline. The Alzheimer‘s Association —Maintain Your Brain campaign recommends mental activity as a key component of a —brain healthy lifestyle. In addition, the Alzheimer‘s Association recently partnered with the Centers for Disease Control and Prevention to develop the —Healthy Brain Initiative, which recommended studying the effects of mental activity on maintaining/improving cognitive functioning. The Alzheimer‘s Drug Discovery Foundation promotes neurogenesis, rather than treatment for neuropathology, as a preventive strategy for cognitive compromise. Computerized cognitive training (CCT) is an intervention that has shown promising results in the improvement of cognitive functioning, more consistently in the elderly who are not demented. To date, CCT studies have typically examined only cognitive outcomes, and only shortly after the intervention.

The proposed study will assess longer-term as well as short-term effects of a CCT program, compared with an active control, —classic computerized games. Participants will be non-demented elderly veterans with diabetes mellitus, who are at particularly high risk of developing cognitive impairment, recruited from two VAMCs: James J. Peters, Bronx, NY and Ann Arbor, MI. Six primary outcomes on three levels will be: cognition (memory and executive functions/attention), behavioral (self-reported DM self-management and medication adherence from VA records), and clinical outcome (glycemic and blood pressure control). CCT programs have major advantages: they are multimedia, interactive, performed at flexible hours at the subject‘s residence without a live instructor, and available for use after the training period. Responses are recorded to monitor progress, without data entry problems. The proposed CCT program, Personal Coach from Cognifit (Seattle, WA), is designed to improve cognition of elderly persons by targeting their weak cognitive functions, using a personally tailored training plan. The active control games program provides similarly structured tasks, but was not

designed to improve cognition. The proposed study will further innovate with booster training sessions, which have been found to provide additional cognitive benefits in non-computerized cognitive training programs.

The proposed study initiates an untapped area of research: the evaluation of short-term (6 months) and longer-term (12 months) health benefits of this promising intervention. This study focuses on elderly diabetic veterans, who are at particularly high risk for dementia. If successful, the results will be invaluable for designing a large scale multi-site study to justify clinical implementation of CCT throughout the VA for diabetics, and perhaps eventually for other elderly veterans who are vulnerable to cognitive compromise. The specific aims of this randomized, controlled trial on non-demented elderly veterans with diabetes are: **Aim 1. A)** To determine whether the CCT intervention, relative to the active control games program, improves cognition (memory and executive functions/attention), DM-related behavior (DM self-management and medication adherence), and clinical outcomes (glycemic and blood pressure control), 6 and 12 months after the intervention. **B)** To demonstrate efficacy by improvement in behavioral outcomes (DM self-management and medication adherence) 6 months after the intervention. **Aim 2.** To document the effects of CCT on the successive changes in memory and executive Functions/attention, DM self-management and medication adherence, and glycemic and blood pressure control. **Aim 3.** To explore the impact of demographic (age, education, ethnicity, site) and health (ADL/IADL, health literacy, depression, family history of dementia, lifestyle factors) characteristics, on the intervention effects.

4.0 Resources and Personnel

The James J. Peters VA Medical Center

The James J. Peters VA Medical Center (JJP VA) in the Bronx has a longstanding and active research program, supported by a strong R&D office directed by Dr. Mary Sano, internationally known clinical investigator in Alzheimer's disease and a co-investigator in the proposed study.

The VA Ann Arbor Healthcare System

The VA Ann Arbor Healthcare System has provided state-of-the-art healthcare services to more than 153,000 veterans living in a 15-county area of Michigan and northwest Ohio.

JJP and Ann Arbor GRECCs

Dr. Penrod is an investigator with the JJP GRECC and Dr. Lee is an investigator with the Ann Arbor GRECC, and Dr. Alexander is its director. The Centers' goals are to increase capacity for conducting state-of the- art health services research on care for veterans with complex conditions, such as diabetes, with particular emphasis on care for the elderly. Thus, the proposed project is well within the theme of these centers and the project will be supported by the centers for items such as office space, computer hardware and software for investigators and staff. Desktop computers linked to secure VAMC servers behind VA firewall are available to investigators for data management and analyses with no data kept on individual computers.

We anticipate that most subjects will be assessed at the two VAMCs, where we have rooms for clinical/medical assessments fully equipped with examining beds, sinks, etc. as well as desks for the neuropsychological assessments. Please note that many of these outpatient veterans visit relatively frequently the VA. However, since these are elderly diabetic veterans, who may have difficulties ambulating into the hospital, we will examine them at their residences if they prefer so. All research coordinators will be required to have a car.

Jeremy Silverman, Ph.D., Principal Investigator, is a Clinical Psychologist at the JJP-VAMC with 30 years of experience at the VA. He is also a Professor of Psychiatry in the Department of Psychiatry at the Mount Sinai School of Medicine. Dr. Silverman will be responsible for constructing and implementing ascertainment strategies, monitoring their progress, and

ensuring the quality of the project. He is responsible for the design, and will lead the analysis, interpretation of results, planning of implementation and dissemination processes, and preparation of papers. Dr. Silverman will supervise the recruitment and data collection at the JJP-VAMC. He will lead bi-weekly meetings (the Ann Arbor staff will join on a conference call) to discuss all day-to-day aspects of the study (recruitment, reasons for refusals and ways to overcome them, data entry and missing data, staffing and coordination issues, etc.). Dr. Silverman will confer with the senior staff of the project at least monthly. Dr. Silverman will have access to PHI.

Hillel Grossman, M.D., Co-investigator, is the Director of the Memory Disorders Clinic at the JJP VAMC, an Associate Professor in the Department of Psychiatry at Mount Sinai School of Medicine, and the Co-PI of the Clinical Core in the ADRC. Dr. Grossman will use similar methods to review each case at both sites to ensure that the veterans do not have dementia and meet memory functioning for participation. Dr. Grossman will also be responsible for identification of adverse events at the JJP VAMC. Dr. Grossman will have access to PHI.

Elizabeth Guerrero-Berroa, Ph.D., Co-investigator, is a clinical neuropsychologist by training. She is an Assistant Professor in the Department of Psychiatry at the Icahn School of Medicine at Mount Sinai. Dr. Guerrero-Berroa will be responsible for assisting the PI with training and supervision of research coordinators at the JJP VAMC for the successful implementation of the study procedures. She will assist with study participant recruitment, grants management, and database management. Dr. Guerrero-Berroa will supervise administration, scoring, and data entry of neuropsychological tests at the JJP VAMC and the Ann Arbor VAMC, attend senior investigator meetings, and participate in manuscript preparation. She will have access to PHI.

Joan Penrod, Ph.D., Co-investigator, is Director of the HSR&D REAP "Center for Research on Health Care Across Systems and Sites of Care" housed at the JJP VA. She will be instrumental in the integration of CPRS and other VA databases into the study, particularly for Aim 3, where historical CPRS information will be examined in order to identify sub-groups of veterans that respond best to the CCT. She will be involved in manuscript writing and will participate in the monthly senior investigators' meetings. Dr. Penrod will have access to PHI.

Mary Sano Ph.D., Co- investigator, is a nationally recognized neuropsychologist with a longstanding research interest in cognitive functioning in the aged. Dr. Sano is the Associate Chief of Staff for Research and Development at the JJP VAMC, a Professor in the Department of Psychiatry at the Mount Sinai School of Medicine, and the Director of the Mount Sinai ADRC. She is the PI of several major clinical trials of Alzheimer's disease and will provide this expertise to the proposed study. Dr. Sano worked closely with the PI in the development of the design and the primary and secondary outcome measures for the proposed study. She also advised on the composition of the cognitive assessment battery. Dr. Sano already meets regularly with the PI to discuss projects involving the ADRC and will join the monthly senior staff meetings for this project. Dr. Sano will be involved in manuscript preparation. Dr. Sano will have access to PHI.

To Be Hired, Research Coordinator, will have a psychology or related degree. She/he will be the instructor for the proposed study, training subjects in the use of PCT and computer game programs. She/he will be on call for technical assistance, and will contact participants weekly to identify and resolve technical problems, and record adverse events. The research coordinator will also perform the duties of the JJP-VAMC research assistant described below, but approximately 2 baseline assessments per week. She/he will also recruit, validate the data entry by the JJP-VAMC research assistant, will perform informed consents, and will have access to PHI.

To Be Hired, Research Assistant, will have a psychology or related degree. She/he will be involved in the recruitment effort and the scheduling of participants. He/she will be trained and certified in the CDR and all neuropsychological tests. She/he will participate in the meeting to discuss eligibility of potential participants for the proposed study. She/he will perform approximately 3 baseline or follow up assessments per week and enter the data. She/he will

also validate the data entry by the JJP-VAMC research coordinator. She/he will recruit, perform informed consents, and will have access to PHI.

Pearl Lee, MD., Co-investigator, will be the Ann Arbor site PI for the proposed study. Dr. Lee is a Physician Scientist in the GRECC and Attending Physician in the Geriatric Medicine Clinic at the Ann Arbor VAMC. She is also an Assistant Professor at the Department of Internal Medicine in the Division of Geriatric Medicine, University of Michigan School of Medicine. Dr. Lee will take overall responsibility for the successful implementation and performance of the study at the Ann Arbor site. She will supervise the Ann Arbor VAMC research coordinator and research assistant to ensure smooth implementation of all methods, from recruitment through data entry. She will confer with Dr. Silverman on a weekly basis to monitor progress, and ensure homogeneity in all methods among the two sites. Dr. Lee will lead the Ann Arbor staff meetings, attend the senior investigator meetings, and participate in manuscript preparation. Dr. Lee will have access to PHI.

Neil Alexander, M.D. Co-investigator, is the GRECC director at the VA Ann Arbor Healthcare System. Dr. Alexander will be involved in developing the recruitment strategy at the Ann Arbor site. Dr. Alexander will participate in the joint Clinical Core

Sarah Krein, PhD, RN, **Co-investigator**, is a Research Scientist at the VA Ann Arbor Center for Clinical Management Research, a Health Services Research and Development (HSR&D) Center of Excellence and a Research Associate Professor in the Department of Internal Medicine at the University of Michigan. She is an experienced investigator who is co-Director of the VA's Quality Enhancement Research Initiative for Diabetes (QUERI-DM) Research Coordinating Center. She will be involved in interpretation of the study data, and participate in senior investigator meetings and manuscript writing. In Year 1, Dr. Krein will be involved in setting up the clinical trial. In Year 4 Dr. Krein will also lead dissemination and implementation activities. Dr. Krein will have access to PHI.

To Be Hired, Research Coordinator, will have a psychology or related degree. She/he will be the instructor for the proposed study, training subjects in the use of PCT and computer game programs. She/he will be on call for technical assistance, and will contact participants weekly to identify and resolve technical problems, and record adverse events. The research coordinator will also perform the duties of the Ann Arbor VAMC research assistant described below, but approximately 2 baseline assessments per week. She/he will recruit, validate the data entry by the Ann Arbor VAMC research assistant, will perform informed consents, and will have access to PHI.

To Be Hired, Research Assistant, will have a psychology or related degree. She/he will be involved in the recruitment effort and the scheduling of participants. She/he will be trained and certified in the CDR and all neuropsychological tests. She/he will participate in the meeting to discuss eligibility of potential participants for the proposed study. She/he will recruit, perform approximately 3 baseline or follow up assessments per week and enter the data. She/he will perform informed consents, and will have access to PHI.

Consultants

Michal Schnaider Beeri, Ph.D., is an Associate Professor in the Department of Psychiatry at the Mount Sinai School of Medicine. Dr. Beeri was the PI of the original submission of this proposal, but left the VA to become the Director of the Joseph Sagol Neuroscience Center at Sheba Medical Center in Israel. Dr. Silverman will consult with Dr. Beeri on all aspects of this project.

James Schmeidler, Ph.D., Co-investigator, statistician, is an Assistant Clinical Professor of Psychiatry at the Mount Sinai School of Medicine, where he has collaborated with the PI for over 20 years. He devised the experimental design of this study. In year 1, he will design and write the data management programs. He will supervise data management and statistical analyses by Ms. West. In year 4, he will perform the longitudinal analyes, and interpret cross-sectional and longitudinal statistical results together with Dr Silverman,

and the other senior investigators, and participate in the senior investigator meetings and writing papers. Dr. Schmeidler will have access to PHI.
Rebecca West, M.A., Statistical Programmer, In year 1, she will train the research coordinators and assistants at both sites on instruction of the interventions, and will supervise those activities. She will be responsible for data management, and will oversee acquisition of data from CogniFit, the company providing the computerized interventions. She will produce quarterly reports to be presented in the staff meetings. In year 3, she will perform cross-sectional statistical analyses of the baseline data and the results of the intervention at two months, immediately after treatment. In year 4, she will perform statistical analyses, and prepare tables and figures. Ms. West will be supervised by Dr. Schmeidler, and will have access to PHI.

5.0 Study Procedures

5.1 Study Design

Upon receiving a list of the potential subjects who meet eligibility criteria according to initial screen using the CPRS , we contact their primary care physicians or the chief of the diabetes clinic and ask for their permission to contact their patients. It should be noted that in our prior studies of elderly Veterans, all physicians approved approaching their patients. Subjects will be then sent a letter describing the study, inviting them to get in touch with us by phone or mailing in a postage paid card. Unless a subject replies telling us not to call, the research coordinators will call the subject. That phone call will include a short screening procedure. In this screening, subjects are asked if 1) a doctor has ever told them that they have a memory problem/dementia/Alzheimer‘s disease, and 2) if they have ever received medication to treat a memory problem (the names of all FDA approved medications for Alzheimer‘s disease are presented to the subjects). Additionally, in this phone conversation subjects are asked about all other inclusion and exclusion criteria (availability of an informant to complete brief questionnaires, computer and internet access, familiarity with computer, ability to see and hear computer, information about the computer [operating system]. Potential subjects also complete the diabetes self-management questionnaire on the telephone. Then subjects are scheduled for a face-to-face interview that includes the informed consent procedure. After informed consent, the interview will continue with baseline cognitive assessments, blood draws, and blood pressure measurement (see measures described later). This can occur in one visit or over more than one visit, as preferred by the participant. Subjects will be assessed at their residences or come to their respective VAMCs, according to their preference. Participants are then randomized to their treatment group, and receive a visit (during which they are instructed in how to use the program, and complete the first session of the program. Participants then continue use of the program for a total of 24 sessions, 3 days per week (one session every other day). Once the program is completed, participants are again assessed with cognitive assessments, blood draws, and blood pressure measurement (identical to baseline visit). Four months after completion of program, participants complete a 3-session booster session. Six months and twelve months after completion of the program, they again complete the cognitive assessments, blood draws, and blood pressure measurement (identical to baseline visit).

Procedures:

Cognitive testing- After informed consent, the interview will continue with baseline cognitive assessments, blood draws, and blood pressure measurement. Subjects will be assessed at their residences or come to their respective VAMCs, according to their preference. The Clinical Dementia Rating (CDR) scale, Mini Mental State Exam (MMSE), and Neuropsychological evaluation will be utilized for cognitive testing (see details of these tests below).

Interventions- Randomization and training for use: At each site, a computer program will randomize the order of the CCT and the games program, within 100 consecutive pairs of eligible subjects. At an initial home visit, an instructor will install the computer program and provide individual instruction with a single standardized script for both programs. The instructor will be a research coordinator who is proficient in installation and adjustment of computer equipment and software. The instructor will verify that subjects are capable users of the mouse and keyboard, can read the screen effectively, hear the auditory signals, and perform all procedures. During the training, the instructor will contact subjects weekly, to identify and resolve technical problems and record adverse events, and also be available for technical assistance by phone, 8am to 6pm, seven days a week, and at home if necessary. The Personal Coach software company, Cognifit, provides technical support for the instructor 24 hours a day seven days a week. Subjects and assessors, who administer and score the outcome measures, will be blinded to the intervention. Subjects will be asked not to discuss their computer program with the assessors; the instructor will not be involved in assessment. Since occasional participants may be deemed ineligible after assignment due to inability to perform the computer-based tasks, the next eligible recruit will be the replacement. Thus, randomization will continue until 100 participants in each intervention at each site begin training.

Programs-

Personal Coach- This software package creates, administers, and scores an individually tailored program that emphasizes training to address the cognitive weaknesses of the participant that were assessed prior to training. Thus, it determines the composition of cognitive tasks to be presented throughout the training sessions, based on participants‘ relative performance in the Neuropsychological Examination (NE). The NE is a two-session assessment of a profile of 14 cognitive domains trained by the program: awareness, inhibition, spatial perception, visual short term memory, working memory, hand-eye coordination, visual scanning, response time, divided attention, time estimation, visual perception, shifting, naming, and planning. . Personal coach uses an algorithm that adjusts and customizes the training program by scoring the 14 cognitive domains, based on the pre-training NE, and assigning task frequencies so that the cognitive domains with the lowest NE scores are relatively over-represented. For example, a subject who demonstrates weakness in spatial perception, but scores high in response time in the pre-training NE, will be provided with training sessions including more tasks intended to improve spatial perception, and fewer tasks intended to improve response time. Personal Coach also adjusts the difficulty level for each task, to reflect the participant‘s capability and performance in the previous session. This adaptive-interactive system focuses on cognitive domains with the greatest potential for improvement, and also avoids frustration due to tasks that are consistently too difficult or easy.

Subjects‘ training sessions are 20 minutes in duration. Subjects are instructed to have sessions 3 days per week (every other day), with a day rest between sessions, for a total of 24 sessions.. Personal Coach utilizes 21 tasks.

The NE is an evaluation used by Personal Coach to customize the training for participant‘s need, and also assessed after the eight-week training on the same measures, as a built-in component of the Personal Coach CCT package. We emphasize that the NE is NOT one of the outcome measures of this study—which were independently selected by the investigating team.

Active control classic games program- The proposed control intervention is comprised of games commonly at community centers for seniors, on the internet, or on home computers. The active comparison intervention, unlike a passive comparison or paper and pencil games, was chosen so that the procedures for the two groups would be as similar as possible, facilitating blinding of subjects. The proposed games program is provided by the same software company, Cognifit, as Personal Coach. In both the CCT and the active control, participants receive identical pre-training instruction; are assessed with the NE at the beginning and end of

the program; and complete 20-minute cognitive training sessions, 3 days a week (every other day), with one day rest between sessions, for 24 sessions. The number, distribution, and length of the active control sessions are identical to the CCT; as in the CCT program, computerized feedback and encouragement are provided in each control session. A research coordinator will be available for technical assistance – at home if necessary, and will telephone subjects weekly to ask if they needed any help and if they are performing the intervention. In contrast to the CCT, the active control is not personalized, so the twelve classic computer games included in the control program are presented in a predefined order for all participants with three games in each session.

Booster week- A booster week will be performed at 6 months after baseline (4 months after completion of training), to maintain the improvement in cognitive and other abilities. All subjects will perform a regular training week, i.e. three sessions of 20 minutes each. The CCT subjects will perform the last week of the training and the control games subjects will similarly perform the last week of games they have played during the training.

Blood draw and blood pressure-

Glycemic control will be assessed by drawing bloods from subjects at every assessment. 5 uL will be drawn and assessed using the same machine readings used in our studies both at the JJP and at Ann Arbor (Siemen's DCA Vantage Analyzer). Change from HbA1c at baseline will be calculated at each of the three subsequent assessments. Change in status will be evaluated relative to baseline (same, lower, higher).

Blood pressure measurements will also be performed at every assessment by the research coordinators, using the same machine readings used in our studies both at the JJP and at Ann Arbor (Omron HEM-780). The outcome measures will be changes in blood pressure (systolic and diastolic) from baseline to each subsequent assessment.

Additional assessments: Diabetes self-management and medication adherence, Cognitive Self-Report Questionnaire, Prospective memory tasks, Activities of daily living (ADL) and instrumental ADL, The Geriatric Depression Scale, Sociodemographic characteristics, Health Literacy, Family history review, Lifestyle assessments, Historical data from CPRS, Prior experience with computers , and gait assessments.

There is minimal risk in this study, and no reasonable steps to further reduce harm could be taken. The overall risks of this proposal are slight. Protection of patient confidentiality and privacy will be rigorously guarded by the assignment of coded numbers to each file in the computer database. Professional treatment will not be altered or modified for research purposes. Subjects will be told that all information obtained is confidential and that their participation or non-participation will not affect their treatment.

Subjects will be told that information which identifies the subject will not be shared with any collaborator, parties outside of our immediate research laboratory, nor family member. Subjects are informed that they may terminate testing or training at any time should they find any aspect objectionable. The interviewers and research assistants will be clinically trained and will be sensitive to signs of stress, anxiety and/or fatigue.

Interviews and assessments will be terminated should any subject show signs of discomfort. We will make every effort to protect the subject's confidentiality. However, subjects will be told that should such information be accidentally disclosed to the wrong party, it could possibly have adverse consequences for the subject in terms of liability in legal proceedings, or discrimination in obtaining life or health insurance.

Adverse events will be monitored weekly through phone calls of the instructor to the subjects. The risks in this study are minimal and it is highly unlikely that the proposed protocol will contribute to any adverse outcome. However, the participants will be of advanced age so it

is possible that a participant may die or be hospitalized during the course of the study. Adverse events will be reported according to the timeline in the Table of Reporting Requirements.
As a result of the cognitive assessment at baseline, potential subjects may be excluded from the study due to impaired cognition (by MMSE or CDR) or dementia diagnosis. Similarly, at follow up interviews, subjects may show impaired cognition. With patient permission, we will confer with the primary care physician on any potential medical or cognitive problems.

Risks of this project to the subjects are judged to be very slight. Important new knowledge on the effect of cognitive interventions on cognitive functioning is expected to be gained. It is anticipated that this information will lead to highly beneficial interventions for the diabetic aging population, for whom cognitive decline is a significant concern as well as a public health issue.

The possible direct benefits to those participating in this study are those that might arise from a comprehensive cognitive examination, and from cognitive training. The assessment may provide clinically relevant information and lead to referrals for otherwise unrecognized cognitive problems that may require treatment. The training may provide improvements in cognitive functioning. For these reasons, the slight risks to subjects are reasonable in relation to the anticipated benefits to subjects and others.

Four hundred subjects will be assessed for participation in an 24 session computerized cognitive training program (Personalized Computer Training- PCT) or computer games program. Subjects will be elderly veterans 55+ years old, nondemented, and diagnosed with type 2 diabetes with less than optimal diabetes self-management (i.e. 18 or less on the self management scale). Subjects will not have neurological or psychiatric conditions that might affect cognition (such as Parkinson's disease or Schizophrenia). Subjects must have sufficient vision and hearing to be able to perform the training programs.

Informants: For each subject, we require identification of an informant with contact averaging weekly, who can knowledgeably answer a questionnaire about the subject's day-to-day function and ability to take care of his or her diabetes management. Approximately 400 informants will be contacted via telephone.

Family members: Subjects will be questioned about their family history, including parents and siblings, regarding mental and physical health. These family members will not be contacted in any way.

Research data may be used in the future to develop larger projects, so data will be stored indefinitely. Blood samples will not be banked.

5.2 Recruitment Methods

400 total veterans will be recruited for this study.

In the proposed study, we will take advantage the following methods to recruit subjects: Upon receiving a list of the potential subjects via CPRS (using a method already with IRB approval at the local VAMC of the PI: James J Peters VAMC) who meet eligibility criteria according to initial screen using the CPRS, we contact their primary care physicians and ask for their permission to contact their patients. It should be noted that in our prior studies of elderly Veterans, all physicians approved approaching their patients. Subjects will be then sent a letter describing the study, inviting them to get in touch with us by phone or mailing in a postage paid card. Unless a subject replies telling us not to call, the research coordinators will call the subject. That phone call will include a short screening procedure—with no preserved documentation of these responses, a procedure already approved by the local VAMC IRB—in order to minimize recruitment of subjects with more than mild cognitive impairment. In this screening, subjects are asked if 1) a doctor has ever told them that they have a memory problem/dementia/Alzheimer's disease, and 2) if they have ever received medication to treat a memory problem (the names of all FDA approved medications for Alzheimer's disease are

presented to the subjects). Additionally, in this phone conversation subjects are asked about all other inclusion and exclusion criteria, such as diabetes management and computer use. Then subjects are scheduled for a face-to-face interview that includes the informed consent procedure.

Potential participants will be identified using data from VISTA/CPRS. In addition, at Ann Arbor VA there is a registry as part of PACT demo lab activities as well as the capacity to automatically extract the requisite data to compile a list if needed.
Research team members may also approach the doctors and other staff and ask them for referrals. Finally, we will post flyers and, possibly, advertise in local newspapers, and will sponsor educational programs regarding the cognition and diabetes directed to Veterans.

Participants will be reimbursed for their time and effort devoted to the study with a check, $50 for the baseline neuropsychological assessment, $35 for the third visit, $50 for the fifth visit and $50 for the 6th. The local VAMCs: the James J Peters VAMC in the Bronx NY and the Ann Arbor VAMC will individually dispense payment to their participants. Participants will be reimbursed for their time and effort after each neuropsychological assessment. Checks will be requested for each participant immediately after completion of an assessment, to limit wait time. Informants will not be reimbursed, due to budget restrictions and the brief nature of their involvement.

5.3 Informed Consent Procedures

Participants will provide information in person in their homes, or at the local VAMC. Participants will provide information through the memory and cognitive assessments, and only research staff members will receive and use that information. Participants are not likely to feel any stigma in entering the VAMC or hospital, or within their own homes. In nearly all cases, the participant will already be a patient at that VAMC and will regularly be seen by doctors there. The information collected is not likely to cause any discomfort, but efforts will be made to clearly communicate to the participants that their information is confidential. Participants will also be informed that they may refuse to answer any questions that make them uncomfortable. Only investigators and staff listed on this project will be allowed to view any identifiable information about the participants. These individuals will have completed their IRB certifications. All efforts will be made to make participants comfortable in the research setting. Most participants will be seen in their homes or at the VAMC where they are regular patients; this should help ensure their comfort. We will inform all participants that they may refuse to answer any questions that make them uncomfortable. Research coordinators and assistants, who will have completed all required human subjects protections training and will have met with the PI regarding how to collect informed consent, will be obtaining consent, and as we are only recruiting and enrolling those with capacity to consent, we do not anticipate any issues with regards to capacity to consent. Each local site PI will meet with their research team members to discuss the consent, the information provided in the consent, and how to properly review the consent with participants, at an "informed consent procedures" meeting prior to the start of the research study.

We are requesting a waiver of documentation of informant consent and a waiver of HIPAA authorization. In order to perform a CDR (Clinical Dementia Rating Scale) informant interview and diabetes management interview over the telephone. Our procedure is as follows:

1. We meet with the participant, consent them, and request permission to speak with an informant.
2. The participant contacts their informant and asks this informant to contact us by telephone, or to agree to be contacted by us, to complete the informant interview; name and telephone of the informant are collected to be in contact with the informant.

3. The informant completes the consent form over the phone (as there is no need to see the informant in person), with a waiver of signature.

Please note that subjects will be informed prior to signing the consent that an informant is required, so that any participant not interested in providing an informant will know before signing a consent, so that they may choose not to participate.

Further, this study includes a family history assessment that collects information about memory disorders and ages of relatives (living and deceased) of the participants in this study. It would be impractical to attempt to contact all first-degree relatives, and some of these relatives are deceased. We will be gathering information about family members (both demented and not), through the participants themselves, that would be collected during a routine complete medical history, only collecting first initials and no other identifying information. We are requesting a waiver of HIPAA authorization and of informed consent.

5.4 Inclusion/Exclusion Criteria

1. 55 years old or above.
2. A diagnosis of type 2 diabetes.

Inclusion criteria 1 and 2 are major foci of the study- a study of cognitive training in the elderly with diabetes.

3. Does not have dementia or prescribed AD medications. This is to aid in confirmation of cognitive health
4. Does not have major medical, psychiatric, or neurological conditions that affect cognitive performance. This will ensure time and ability to take part in the study.
5. Home access to computer and internet.
6. Has an informant. This is to aid in confirmation of cognitive health.
7. Self-management score 18 or below. Self-management is a focus of the study.
8. Does not have severe impairment of vision or hearing. This will ensure ability to take part in the study.

Anyone not meeting the above inclusion criteria will not be enrolled.

5.5 Study Evaluations

The below-described materials are included as an appendix to this document.

In the pre- screening, subjects are asked if 1) a doctor has ever told them that they have a memory problem/dementia/Alzheimer‘s disease, and 2) if they have ever received medication to treat a memory problem (the names of all FDA approved medications for Alzheimer‘s disease are presented to the subjects). Additionally, in this phone conversation subjects are asked about all other inclusion and exclusion criteria.

Cognitive testing- After informed consent, the interview will continue with baseline cognitive assessments, blood draws, and blood pressure measurement. Subjects will be assessed at their residences or come to their respective VAMCs, according to their preference.

1. Clinical Dementia Rating (CDR) scale: Severity of cognitive and functional impairment is assessed from subject information and an informant (someone with contact averaging weekly, who can knowledgeably answer a questionnaire about the subject’s day-to-day function and ability to take care of his or her diabetes management).Only non-demented subjects, with a CDR of 0 (no dementia) or 0.5 (questionable dementia), are eligible.
2. Mini Mental State Exam (MMSE): This 30-item questionnaire assesses orientation, concentration, memory, and language. A score 25 is an exclusion.

3. Neuropsychological evaluation: Cognitive performance is assessed by the Unified Data Set (UDS 2.0) neuropsychological battery used by the ADRC with some additional tests. This battery was designed independently of the Personal Coach neuropsychological exam (the NE) and has been used in many of our studies of cognitive aging. The neuropsychological evaluation can be conducted in approximately 60 minutes and includes the following tests (organized by cognitive domain):

i. Memory. There are two types of verbal memory tasks; word list and paragraph recall.

(1) Word List Memory- This is a free recall memory test that assesses learning ability for new verbal information. Participants are presented 10 unrelated items on printed cards to read aloud. Immediately following presentation of all 10 words, the participant is asked to recall as many as possible. On each of the three learning trials, the 10 words are presented in a different order. The maximum score on each trial is 10. The maximum total score for *immediate recall* is 30. *Delayed recall* tests the ability to recall, after 15 minutes, the 10 words given in the word list memory test. The maximum number of correct responses is 10. Word list *recognition* counts the number of 10 words presented in the word list memory task correctly recognized (Rec-yes). These words are presented among 10 distracter words. The number of distracter words correctly identified (Rec-no) is also counted. The maximum score for each is 10.

(2) Paragraph recall: this task is the Logical Memory subtest of the Wechsler Memory Scale-III. We will use the 2 stories for immediate recall and for delayed recall, 20 minutes later. The maximum score for each is 25.

ii. Attention/Executive Functions.

(1) Target Cancellation Tests: These tests will be used to assess vigilance and speeded attention. They require subjects to identify target stimuli randomly interspersed among distractor stimuli on a sheet of 8.5-by- 11 paper. One task requires the subject to identify diamonds among other geometric figures, and another to identify a specific triple of letters (TMX) among other triples of letters. The measures are the numbers of correct targets identified in four minutes.

(2) Trail Making Test: The Trails tests measure timed attention, mental flexibility and sequencing. Part A entails connecting randomly ordered numbers by drawing a line in sequence. Part B entails connecting numbers and letters in alternating order (i.e. 1, A, 2, B, etc.). Although number of errors in each part will be recorded, the analysis will include only the two time measures.

(3) Digit Symbol Substitution Test: The subject is given a key grid of numbers and matching symbols and a test section with numbers and empty boxes. The test consists of filling as many empty boxes as possible with a symbol matching each number. Time is 90 seconds, and the score is the number of correct number-symbol matches.

(4) Digit Span: This is a subtest of the WAIS-III. The Digit Forward section assesses attention by reading sequences of digits to the subject for immediate verbatim repetition. Then the Digit Backwards section consists of sequences to be repeated in reverse order. The numbers of correct answers in the sections will be the two measures used for the analysis.

iii. Language

(1) Similarities. Similarities is a subtest from the WAIS-Revised. The test measures abstract thinking by asking the subject to state how pairs of words (e.g., egg/seed) are alike. The number of correctly answered pairs is the single measure from this test with maximum score 33.

(2) Boston Naming Test: It assesses the ability to name 15 black and white line drawings representing a range of high to low frequency English words. The number of correctly identified drawings is the single measure.

(3) Category fluency: Subjects will be asked to generate exemplars in two categories: animals, and fruits and vegetables; 60 seconds are allowed for each category. The score is the sum of the numbers of correct exemplars in the two categories.

(4) Controlled Oral Word Association Test (COWA): In three one-minute trials, this test of phonemic fluency assesses the ability to name as many words as possible beginning with three letters—F, A, S. The single measure is the sum of words in all three trials.

Blood draw and blood pressure- Glycemic control will be assessed by drawing bloods from subjects at every assessment. 5 uL will be drawn and assessed using the same machine readings used in our studies both at the JJP and at Ann Arbor (Siemen's DCA Vantage Analyzer). Change from HbA1c at baseline will be calculated at each of the three subsequent assessments. Change in status will be evaluated relative to baseline (same, lower, higher). Blood pressure measurements will also be performed at every assessment by the research coordinators, using the same machine readings used in our studies both at the JJP and at Ann Arbor (Omron HEM-780). The outcome measures will be changes in blood pressure (systolic and diastolic) from baseline to each subsequent assessment.

Diabetes self-management and medication adherence- A self-report scale of diabetes self-management collects five separate areas of diabetes self-care (medication adherence, exercising, following an eating plan, blood glucose monitoring, and foot care), subjects will be asked —"Over the past year, how difficult has it been for you to do each of the following, exactly as the doctor who takes care of your diabetes suggested?". Labels on the five response categories (scored 0 – 4) range from —"So difficult that I couldn‘t do it at all" to —"Not difficult, I got it exactly right." Subjects can also respond that the area of diabetes care is —Not applicable for them. Possible scores for the scale range from 0 to 20, with higher scores meaning greater self-management in the five domains. Like the assessment of the CDR, which is based on both subject and informant interviews, the DM self-management questionnaire will also be administered to the informant and the scores for each item – averaged from both sources – will be summed.

Cognitive Self-Report Questionnaire- This questionnaire assesses perceptions of cognitive abilities and will be administered before and after training (together with each neuropsychological assessment). The CSRQ-25 consists of 25 statements about cognition and mood in everyday life over the past 2 weeks, answered using a 5-point Likert scale.

Prospective memory tasks- Since diabetes medication is taken at specified times, we will employ time-based prospective memory items from the Rivermead Behavioural Memory Test (3rd Edition) to assess this type of memory.

Activities of daily living (ADL) and instrumental ADL- The ADL questionnaire has eight yes/no items covering the following activities: dressing, grooming, rising, eating, walking, hygiene, reaching, and gripping. Similarly, the IADL questionnaire has three yes/no items covering the following activities: making financial transactions such as paying the bills, running errands and shopping, doing chores such as vacuuming and yard work. For each questionnaire the total number of items endorsed will be split at the median to define sub-groups.

The Geriatric Depression Scale- The Geriatric Depression Scale (GDS) is a 30-item self-report yes/no questionnaire on feelings of general satisfaction with life, expectations of the future, boredom, activity levels, anxiety, fearfulness, ability to concentrate, energy levels, and sadness. A score above 14 is interpreted as indicating clinically significant symptoms and will be used to define sub-groups1.

Sociodemographic characteristics- Education and age will be collected.

Health Literacy. The Short Test of Literacy Functional Health Literacy in Adults (S-TOFHLA) will be used to assess health literacy. In this test, subjects read passages in which every fifth to seventh word has been deleted and subjects are asked to insert the correct word from a choice of four words. The short version involves only two reading comprehension sections.

Family history review- we use the well validated dementia family history questionnaire. Information regarding the birth year, age or age of death, cause of death, and any physical or

mental illness is collected for all first-degree relatives. If the subject reports that a first-degree relative has/had dementia or memory problems, the Dementia Questionnaire is then used to clarify a diagnosis of dementia.
Lifestyle assessments- Smoking history will be collected, and the physical activity questionnaire provides six levels of activity, from mostly sitting to strenuous exercise several times a week.
Historical data from CPRS- Directly measured HbA1c and blood pressure will be clinical outcome measures. We will additionally take advantage of CPRS data and explore whether historical HbA1c and blood pressure, i.e. the average HbA1c and blood pressure in the last three years prior to the intervention, predict benefits from the CCT.
Prior experience with computers- Prior experience with computers will be assessed at baseline.
Diabetes Care Profile-The Diabetes Care Profile is a self-administered instrument that assesses the social and psychological factors related to diabetes and its treatment. For this study, we have adapted the approximately 40-page questionnaire to 13 pages. Participant responses are scored using various scales including understanding, support, attitude, and care ability. This is administered everytime the neuropsychological assessments are completed.
Vision Screen-To formalize the assessment of the veteran's capability to use the computer, we implemented the Vision Screen, which seeks to determine whether or not the veteran has any visual issues, and if so, if there issues have been addressed by a medical doctor or affect daily tasks that require adequate vision. In addition, we also use this form, to gauge the participant's ability to adequately use the computer and the CCT program—that is, to use the mouse, and to understand the instructions.
End of Program Survey- This survey captures the participants' experiences with the computerized cognitive training program.

Gait assessments:

WALKING WHILE TALKING (WWT)
The WWT is a cognitive-motor divided attention task (Dual Task) that has been shown to uncover "subclinical" gait deficits, by increasing the complexity of the walking condition. Participants are asked to walk while reciting alternate letters of the alphabet. The test measures both the time (seconds) taken by an individual to walk a distance of 6 meters, and the accuracy of the cognitive responses (#correct responses/total responses) during the walk. It consists of 3 components: Single Task Cognitive; Single Task Walk; and Dual Task Walking while Talking. Participant should wear their regular footwear and use their customary walking aid (none, cane, or walker). No physical assistance is given.

Single Task Cognitive
Description: Single task cognitive performance is assessed by asking participants to recite alternate letters of the alphabet(i.e. a, c, e,…etc), while standing still for 10 seconds. Two trials are performed, the first beginning with the letter 'A' and the second with the letter 'B'.
Record for each trial: Responses generated within each 10 seconds interval. Response accuracy is the single task cognitive outcome and is calculated by dividing the number of correct responses by the total number of responses.

Single Task Walk:
Description: Single task walking performance is assessed by timing. The participantstands behind the walkway start line,and at the command "GO", walks down the walkway at their normal, comfortable pace, stopping after crossing the deceleration line. For safety, the

examiner walks to the side and slightly behind the participant, being careful not to pace the participant.
Record for each trial: Time, in seconds, to complete the central, 6 meter portion of the walkway. Timing begins when the participant's foot crosses over the 1st white line and ends when their foot crosses the 2nd white line. Note whether an assistive device is utilized to perform the task. Speed (meters per second) is the single task walk outcome and is calculated by dividing the distance (6 meters) by the time taken to walk it. A value is calculated for each trial.

Dual Task Walking While Talking:
The WWT consists of walking the designated walkway while simultaneously reciting alternate letters of the alphabet. The participant walks down the 8 meter walkway, at their normal, comfortable pace, while reciting alternate letters of the alphabet. The participant is instructed to pay equal attention to both the walking and cognitive task. Testers do not advise or encourage subjects during the task, intervening only in situations where subject safety is an issue. The initial letter in the cognitive task is randomly varied between (C-E-G) in the first trial and (B-D-F) in the second trial at subsequent time-points to reduce learning effects. Participants continue reciting letters until they have completed the walking task-they do not end when they reach the end of the alphabet. For safety, the examiner walks to the side and slightly behind the participant, being careful not to pace the participant.
Record for each trial: Time, in seconds, to complete the central, 6 meter portion of walkway and the letter responses generated during the duration of the walk.

5.6 Data Analysis

Data analysis
We will examine all variables for errors. Substantially non-normal distributions will be transformed to reduce the influence of extreme values. SPSS or SAS will be used aims 1 and 3, and Mplus will be used for Aim 2.

Linear mixed model analyses for Aims 1 and 3- These analyses will be intent-to-treat (ITT) comparisons of the 150 subjects randomized to the CCT with the 150 randomized to the control intervention, with four observations — baseline, at 2 (end of treatment), and 8 and 14 months afterwards (post-treatment). Linear mixed models (LMM) will be fitted for two endpoints, the 8 and 14 month observations. Missing data will be accounted for using iterative full information maximum likelihood estimation of the relevant model parameters. For Aim 1, each model will include intervention group and time as fixed factors, subjects as a random factor, and – most importantly – the intervention group by time interaction, which indicates whether the change in outcome over time differs between the intervention groups. To reduce variation attributable to subject differences, and to control for possible unbalanced randomization by age, sex, education, or baseline MMSE, these will be included as primary covariates. With regard to other, secondary covariates, such as ethnicity, health literacy, or computer experience, if any correlates with an outcome at $p<0.05$, it will be used as a covariate in a secondary analysis, to reduce within-group variation. The number of intervention sessions completed will be a covariate in secondary analyses. To confirm the results, for each post-intervention assessment, ANCOVAs will test group differences in changes from baseline to the post-intervention observation, using the baseline score as a covariate.

For Aim 3, the LMM model will also be used to explore the contributions of demographics (age, education, ethnicity) and health-related characteristics (health literacy, ADL/IADL, depression, family history of dementia, smoking and physical activity habits; see section D13 of the grant) to the effects of CCT on each of the primary and secondary outcomes, by including them in the analyses. We will add the characteristic as a covariate, and also its

interactions with the intervention group by time interaction and lower order interactions. Identifying the contributions of such characteristics may suggest underlying mechanisms of CCT efficacy, in addition to targeting subgroups of subjects for whom the intervention is most efficacious. This may guide planning of dissemination and implementation of a CCT program (see section E). For descriptive purposes, we will compare the interventions using dichotomized subgroups of the characteristics (e.g., low and high education).
Significance levels for multiple outcomes and for efficacy analysis. The six primary outcome measures for Aim 1A are memory and executive functions/attention, diabetes self-management scale and medication adherence, and glycemic and blood pressure control. Each of these variables will be a dependent variable in two LMM analyses, for follow ups at 6 and 12 months after the intervention. Although demonstration of benefit of CCT beyond that of the active control is directional, tests of significance will be two-sided, for sensitivity to the possibility that CCT is substantially inferior to the active control. Each of these results will be critical for designing a large scale multi-site study to justify clinical implementation of CCT throughout the VA, so each will be tested at the 0.05 level. Similarly, each of the Aim 3 analyses will be tested at the 5% level, since they are all exploratory, for the purpose of identifying Veterans who are most likely to benefit from CCT. For the specific purpose of demonstrating efficacy in Aim 1B, a test of significance of CCT efficacy for noncognitive outcomes, we have selected two of these LMMs, the behavioral outcomes (DM self-management and medication adherence) at 6 months after the intervention, which are intervening variables for the clinical and longer-term outcomes. For this evaluation of efficacy, each of these two LMMs will have a one-sided test, at the 0.025 level of significance. By the Bonferroni inequality, this has a 0.05 upper limit for probability of rejection by chance if the null hypothesis, equivalent to a single two-sided test at the 0.05 level. Path analyses for Aim 2. To compare the linkages through which the two interventions successively affect changes in cognition, behavior, and clinical outcomes, four parallel path analyses (for CCT and active control interventions, at six and 12 months after the intervention) will be performed for the model . Comparisons of the coefficients in the models will indicate whether the CCT has different linkages from the active control intervention.

Power analysis is provided for Aim 1 based on the LMM model, calculated using Equation 15 in Oakes and Feldman. In a study finding significant differences between Personal Coach and a computer games program in a sample of patients with MS25, the effect size for the memory composite was the strongest, 0.97, and most of the effect sizes for other cognitive assessments (tests and composite scores) were between .25 and .30. In addition to the effectiveness of CCT, the power reflects the postulated R2, the proportion of the total variance among the post-test scores that is explained by the pre-test scores. When the pre-test scores predict the post-test scores well (high R2), there is relatively little —noisell so one can clearly discriminate between the two interventions. When R 2 is small, a larger effect is required for detectability. Table 9 in the protocol (grant) displays the effect sizes (differences between the post-test z-score mean in intervention group and the post-test z-score mean in the control group, adjusted for pre-test scores) that are detectable with 80% power using a 2-sided α=0.05 with n=112 participants in each of the two groups. These power analyses demonstrate satisfactory detectability for these effect sizes and R2 values. Thus, samples of n=112 subjects who complete all four assessments provide at least 80% power to detect an effect size for a cognitive outcome in the range of .25 to .30 if R2 is no less than 0.35. Based on a 14-month attrition rate of 25%, a conservative sample of 112 with complete data implies an initial sample of 150 in each group. With such a large sample size, it is seen that the effect size does not depend much on R2, so that even for lower R2=0.30, the detectable effect size is only 0.32. If the effect size is larger, as was observed for memory, the power will exceed .80. To the best of our knowledge, disease self-management and the other behavioral and clinical measures have never been examined as outcomes in the context of CCT, so data suggesting effect sizes is lacking. (Among all other

innovations, the proposed study will also provide data on this.) Effect sizes for a variety of other non-cognitive outcomes in other cognitive training studies (0.50 for gait velocity three months after initiation of the program, in a Personal Coach study, 0.21 for health-related quality of life two years after training in the ACTIVE study, and 0.25 on average, depending on the training modality, for an ADL outcome five years after training in the ACTIVE study) suggest that the effect sizes anticipated for the primary cognitive outcomes will be broadly applicable to the noncognitive outcomes of Aim 1 as well, so power will be comparable. This power analysis for a two-sided test at the 0.05 level also applies to each of the one-sided tests for efficacy in section D16b of the grant. Since this power is based on only one of the two outcomes being efficacious, it provides a conservative power estimate for efficacy based on testing two outcome measures. Although M-Plus also calculates power for comparison path coefficients, the specification of estimates would require an additional level of speculation beyond the speculation for the power analysis of Aim 1. The present proposal will provide the first empirical results on the relationships among changes in cognition, diabetes-related behavior, and clinical outcome in a CCT and in an active control.

Missing data from training dropouts- Since few subjects refuse to continue our longitudinal studies, we anticipate almost all subjects who start the intervention will complete the identical neuropsychological follow up assessments for this study, at the same follow up times, even if they drop out of the intervention.

Statistician James Schmeidler, with the assistance of Rebecca West, will complete data analysis during and after the study, from offices at the JJP VAMC and Mount Sinai School of Medicine.

5.7 Withdrawal of Subjects

Although normal cognitive functioning is a requirement at the start of the study, participants who experience cognitive decline during the course of the study will not be removed from use of the cognitive training program.. If the worsening of cognitive functioning brings a participant to the point of potentially impaired decision-making capacity, they will be discontinued from the study. We have changed the documentation to explain that if decision-making capacity is lost, the follow-up memory and thinking tasks, blood draw and blood pressure tests, and other assessments will not continue. However, a participant may continue using the cognitive training program, they will not be required to stop use of the program. The cognitive data up to the point of potential loss of decision-making capacity will be retained, and when data analysis is conducted, the participant will be marked as having declined in cognitive functioning. Data analysis procedures will be conducted such that it is clear that these individuals, even if they go on to complete the cognitive training, had declined in cognitive functioning and lost capacity. Information regarding actual use of the program by these participants will be incorporated into the analysis.

Subjects are informed that they may terminate testing or training at any time should they find any aspect objectionable. The interviewers and research assistants will be clinically trained and will be sensitive to signs of stress, anxiety and/or fatigue.

6.0 Reporting

Safety monitoring for adverse events (AEs) will be conducted in real time by the PI, research coordinators, and the Central, and JJP and Ann Arbor VAMCs IRBs. All adverse events (serious adverse events (SAEs), unexpected AEs, and expected AEs) will be indicated on the source documentation for the study, and on the specific VA Central IRB adverse event report form. All AEs will be reported to the VA CIRB within according to the Table of Reporting Requirements (within 5 business days when required of the investigative team learning about them, otherwise in summary at continuing review) . The following information about adverse

events will be collected: 1) the onset and resolution of the AE, 2) an assessment of the severity or intensity (use existing grading scales whenever possible), 3) an assessment of the relationship of the event to the study (definitely, probably, possibly or not related), and 4) action taken (e.g., none, referral to MD, start or increase concomitant medication). The PI together with Dr. Grossman at the JJP and Dr. Lee at Ann Arbor will determine the severity of the event, will assign attribution to the event, and will monitor the event until its resolution.

Research staff will maintain communication with participants as part of the study, and will record any reports of an AE, and will ask about any adverse events the participants are experiencing during participation, via regular telephone calls with the participants and at follow-up visits.

After informed consent, participants will be seen in person at baseline, immediately following training (7-8 weeks after baseline), 4 months after completion of training, 6 months after completion of training, and 12 months after completion of training. Participants will be contacted weekly during training. At each of these points, safety data will be collected.

7.0 Privacy and Confidentiality

PHI will be obtained directly from project participants. Upon receiving a list of the potential subjects who meet eligibility criteria according to initial screen using the CPRS, we will contact their primary care physicians and ask for their permission to contact their patients. Subjects will be then sent a letter describing the study, inviting them to get in touch with us by phone or mailing in a postage paid card. Unless a subject replies telling us not to call, the research coordinators will call the subject. Names, SSNs, medical records, ages and birth dates, and telephone numbers and addresses will be collected. The company that makes the two programs, CogniFit, will not have access to personally identifiable information of the participants.

All study data will be securely stored on an approved VA server behind the VA firewall in a folder with restricted access. Only authorized project staff members have access to the folder, and once personnel are no longer a part of the research team, their access to this folder will be removed. Additionally, any identifiable data stored in a crosswalk file are stored in a folder that is separate from datasets to be used for analysis. All analyses files contain a study ID only. Any data to be transferred are transferred using PKI or an encrypted CD, both of which are VA approved methods of transmission. Note that the CCT data is directly sent to the software company every time a subject logs in and off. This data will be connected with an ID number and the training data only and the informed consent will include language that clearly informs the subject this data from the training will be stored at the software company, which is outside the VA. The software provides us with information on number of times the subject logged in, average time on the software, the percent of time subjects performed each task (this variable provides us with information about the cognitive function that was identified by the software algorithm as the weakest and thus was trained the most). Finally, the investigators will NOT provide the software company any information collected by the investigators (such as the neuropsychological assessments performed by the investigating team, medication adherence information, etc.).

Data will also be stored and managed using REDCap (Research Electronic Data Capture). REDCap is currently approved for use, with constraints, by the U.S. Department of Veterans Affairs. We will ensure that we adhere to the constraints outlined by the decision on 1/31/016: http://www.va.gov/TRM/ToolPage.asp?tid=6453&tab=2&minYear=2016.

De-identified will be placed on a regular CD and snail mailed or emailed to Dr. Schmeidler, whose offices are at the Mount Sinai School of Medicine, for data analysis. The PI will ensure that data is backed-up in the event that these de-identified data are lost in transit. Protection of patient confidentiality and privacy will be rigorously guarded by the assignment of coded numbers to each file in the computer database.

Participants will provide information in person in their homes, or at the local VAMC. Participants will provide information through the memory and cognitive assessments, and only research staff members will receive and use that information. Participants are not likely to feel any stigma in entering the VAMC or hospital, or within their own homes. In nearly all cases, the participant will already be a patient at that VAMC and will regularly be seen by doctors there. The information collected is not likely to cause any discomfort, but efforts will be made to clearly communicate to the participants that their information is confidential. Participants will also be informed that they may refuse to answer any questions that make them uncomfortable. Only investigators and staff listed on this project will be allowed to view any identifiable information about the participants. These individuals will have completed their IRB certifications. All efforts will be made to make participants comfortable in the research setting. Most participants will be seen in their homes or at the VAMC where they are regular patients; this should help ensure their comfort. We will inform all participants that they may refuse to answer any questions that make them uncomfortable.

8.0 Communication Plan

Two VA sites are involved in this study, and the study PI and local sites will be in contact regularly regarding any required approvals. Dr. Silverman will lead bi-weekly meetings (the Ann Arbor staff will join on a conference call) to discuss all day-to-day aspects of the study (adverse events or problems, recruitment, reasons for refusals and ways to overcome them, data entry and missing data, staffing and coordination issues, and IRB issues including modifications and ensuring that research is conducted fully within the bounds of the approved IRB protocol). Dr. Silverman will confirm with both local sites that IRB-approval has been fully obtained prior to any conduction of research, or prior to any enacting any modifications of research. Any changes made to IRB documentation will be shared between sites, and IRB paperwork for local sites will be sent to both sites for their records.

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