Computer Assisted Cognitive Rehabilitation Intervention for Persons With Multiple Sclerosis

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PROTOCOL AND PROPOSED STATISTICAL ANALYSIS:

This study will test the effects of an intervention (MAPSS-MS) to promote the cognitive functioning of persons with MS. The effectiveness of the intervention will be examined using a prospective, longitudinal, randomized pretest/posttest usual care comparison group design. The intervention consists of an efficacy-building group intervention that will incorporate an individualized computer-based practice component (CACR) to help participants build self-efficacy for skills to improve cognitive functioning and activities of daily living. The group component of the intervention will provide information specific to cognitive difficulties experienced with MS, help participants assess their difficulties and identify strategies to manage cognitive difficulties and improve performance. The group exercises will focus on helping persons translate the skills they are practicing in the CACR component into everyday life to improve overall functioning and health.

Participants will be recruited from three metropolitan communities in Texas: Houston, San Antonio and Dallas/Fort Worth. The Houston metro area has a population of over 5.9 million persons. The population is approximately 26% white/non-Hispanic, 44% Hispanic, 24% Black, and 6% Asian. The San Antonio metro area has a population of 2.2 million persons; 63% are Hispanic and 7% are African American. More than 6.3 million people live in the Dallas/Fort Worth metroplex; 13% are African-American, 4% Asian or Pacific Islander and 21% are Hispanic or Latino of any race. The Lone Star Chapter of the National MS Society has active offices in each community to support recruitment and implementation.

PI Stuifbergen and Co-I Perez have worked with staff of the Lone Star Chapter of the National MS Society for over 20 years and are well known by MS clinicians throughout the state. The research team has substantial experience with conducting multi-site interventions and data collection (RO1HD035047, R21 NR011076; RO1 NR03195) with persons with MS. Use of the three communities will assure the ability to recruit sufficient participants and support the diversity of the sample (MS predominates in women and whites). Neurologists who are MS Specialists in each community have agreed to assist with recruitment (see letters of support) and serve as consultants for patient referral. The Lone Star Chapter of the National MS Society serves more than 21,000 persons with MS in 174 counties in Texas including these communities.

SAMPLE: The sample for this study will consist of persons with physician-diagnosed MS living in the identified Texas metropolitan areas who are concerned about their cognitive problems.

SAMPLE SIZE: Power analyses were conducted using data from our recent preliminary study. The initial sample size estimate was based upon an f value of .38 for the interaction of time by group for the CVLT-Total. The alpha level was set at .01 to account for the multiple analyses that

are proposed to answer the research questions. A minimum sample of 80 was estimated to have 80% power to detect a statistically significant time x experimental group interaction with a .38 effect size. However, we propose to power the study based upon a lower f value of .28, which corresponds more closely to the effect sizes observed for the other neuropsychological tests. Therefore, 180 individuals will be needed to detect an effect size (f) of .28 as statistically significant. This larger sample size will also provide sufficient power for the more complex 3 site nested design. Based on our preliminary study we estimate that 20% of potential participants who respond to recruitment materials will not meet the inclusion criteria and an additional 25-30% will be unable to attend the classes when scheduled. Thus, we will need to screen 320 persons to recruit a sample of 180 participants (60 at each site). Given the number of participants who consent and do not complete the full data collection we will need to recruit up to 230 persons with MS. The number of persons with MS in the 3 communities is more than sufficient.

INCLUSION/EXCLUSION CRITERIA: To participate, subjects must be diagnosed with MS, age 18 to 60, and capable of understanding and complying with the study protocol. Participants must be able to read and write in English and have visual acuity of at least 20/70 with correction in order to work on the computer screen. All participants must have a clinically definite diagnosis of MS that is documented by their physician. Participants must have stable disease at the time of entry into the study (relapse free for at least 90 days), have subjective concerns about their cognitive functioning (based on the Perceived Deficits Questionnaire), have home internet access, and be willing to participate in an 5 month study involving education/skill building, support and data collection. Participants may be of either gender or any ethnic/racial group. Subjects will be excluded if they have other medical causes of dementia or other neurological disorders that may impact cognition or emotions, evidence of major psychiatric disorder or if they have major functional limitations that preclude them from participating in the study.

RECRUITMENT AND SCREENING: Participants will be recruited in a variety of ways including fliers in offices of physicians, targeted mailings to persons with MS on the mailing list of the National MS Society, contact with support groups, notices in MS newsletters and "word of mouth." Letters of support for recruitment are appended. Recruitment materials will instruct potential participants to call the research office 800 number for additional information about the study. The project staff will have a script to screen potential participants for inclusion/exclusion criteria and will explain the study procedures and requirements to those who are eligible. The Perceived Deficits Questionnaire (Sullivan, Edgley & Dehoux, 1990) will be administered by phone and those scoring indicating they experience at least 5 problems "sometimes" or more often will be eligible to participate. Participants will be asked to provide the name and address of their physician, who will be asked to verify the diagnosis and give a medical clearance for the individual to participate. Recruitment will be ongoing in order to establish a pool of potential participants at each of the three sites. Nine cohorts of 20-22 subjects will be randomly selected (three times at each of three sites) during the study and subjects within the cohort will be randomly assigned (following baseline testing) to the treatment or comparison group. In prior studies, small intervention class sizes (n=10-12) enhanced self-efficacy through vicarious experience and modeling.

Persons who do not qualify to participate in the study based on the screening criteria will be thanked for their interest and receive a brochure from the MS Society on cognitive strategies.

INTERVENTION: MAPSS - MS

The overall purpose of the MAPSS-MS intervention is to help the individual acquire the highest level of cognitive functioning and functional independence. This is accomplished through teaching the use of compensatory skills, retraining skills (the CACR component) and environmental/lifestyle support for cognitive functioning. The MAPSS-MS has two components: (a) Group sessions focused on building efficacy for use of cognitive strategies and (b) an innovative computer assisted cognitive rehabilitation (CACR) program. The home-based computer component will enable the participants to engage in intensive practice sessions without leaving their homes. Translation of skills practiced to everyday issues will be a focus of the group sessions.

Group Component The investigators' prior work will drive the content and process aspects of the MAPSS-MS (Memory, Attention & Problem Solving Skills for Persons with MS) intervention - specifically the health promotion intervention for women with MS (R01HD35047). The intent of the efficacy-based wellness intervention is to engage individuals in assessing their present health behaviors, setting meaningful goals for change and addressing the barriers, resources and skills necessary to improve health behaviors and consequently quality of life. In this study, we will use the same process and strategies (Stuifbergen, et al., 1999; Stuifbergen et al., 2003) to assist participants to acquire knowledge regarding the specific MS-related cognitive impairments; assess and acknowledge their cognitive concerns, build the skills necessary to implement compensatory self-management strategies of cognitive difficulties and set goals for integrating new cognitive skills into their everyday lives.

The group program will consist of weekly 2-hour classes over an 8 week period that present information, guide participants in self-assessment of cognitive problems, resources and barriers to cognitive functioning and enhancing self-efficacy for use of strategies to maximize cognitive functioning. Four major topic areas will be included in the lifestyle change classes (1) Identifying common cognitive problems experienced with MS (2) Compensatory Strategies to Maximize cognitive Skills (3) Maximizing Cognitive Health with a MS – Lifestyle adjustments (e.g. physical activity and energy conservation) to promote cognitive functioning (3) Adjusting to Changes in Cognitive Skills (4) Stress Management (controlling anxiety) and Enhancing Cognition. At each session, the facilitator will evaluate the participants on CACR exercises prescribed at the last session, troubleshoot cognitive strategies and performance difficulties, and prescribe the therapy exercise assignments for the upcoming week.

Computer Assisted Cognitive Rehabilitation (CACR) protocol: In response to the feedback obtained in preliminary studies, we will use the computer training exercises from Lumosity. The computer protocol for this multi-site trial follows:

Computer Protocol: The computer training methodology developed by Lumos Labs, Inc. (San Francisco, CA) uses an open-innovation model targeting effectiveness, designed to adapt to the individual user, offering novel and engaging tasks and challenges within a integrated, hierarchical structure. The Lumosity program has been used in research with childhood cancer

survivors, healthy adults, and older persons with mild cognitive impairment. The Lumosity website (www.lumosity.com) delivers interactive programs and applications that run directly in standard web browsers. Users need only a computer, tablet, or smart phone to access the website and securely log into the program. The PIs will contract with Lumos Labs, (see letter of support) for use of the Lumosity program including development of a suite of specific games/training activities and the collection and delivery of data collected on all participants enrolled in the study. Research staff will register each participant on the Lumosity website using anonymous user ID numbers and passwords allowing participants unlimited access throughout the 8-week intervention period. The delivery of the computer exercises over the Internet allows the participant to complete the exercises from any location on any device with Internet access at any time. During the first group session the facilitator will demonstrate logging on and navigating the website before having the participants practice these skills and work through sample exercises using laptops connected to the internet. As each participant works through a session, the data is saved on the website's servers and the participant is able to start subsequent sessions where he/she stopped progressing in hierarchical fashion. Each participant will be asked to complete a minimum of 45 minutes of training thee times per week and to keep a written log of practice times and dates. The researchers will monitor the skills practiced and the success at various levels via data reports provided via e-mail by Lumos, Labs.

The facilitator will prescribe 2 consecutive weeks of practice with 4 of the Lumosity boost programs addressing the most common problems experienced by persons with MS. The tasks are arranged so that the most basic cognitive skills (attention) are addressed first. As the user progresses, the tasks become more challenging. Each boost is set up in a game like format. The facilitator will be available to participants by phone and email and will contact each participant weekly by phone to assess for any problems using the program.

Weeks 1 & 2 Attention Boost: provides training targeting visual field and focusing. Exercises include: *Lost in Migration*, a selective attention task based on the flanker test paradigm, and *Bird Watching*.
Weeks 3 & 4 Memory Boost: provides training on skills essential to store, retain and recall information, events and procedures. Working memory skills are frequently used to accomplish everyday functioning (using a phone) and evidence suggests that working memory can be expanded and enhanced by practice and the use of compensation techniques. Exercises in the memory boost include: *Spatial Speed Match*, which targets working memory and is based on the n-back working memory paradigm, and *Memory Matrix*, which target spatial memory.
Weeks 5 & 6 Flexibility Boost: provides training on executive function/flexibility skills that play a major role in information processing, abstract thinking, problem solving, initiation and inhibition. Exercises address task switching, which is trained in the Brain Switching game, response inhibition, planning, and verbal fluency.
Weeks 7 & 8 Problem Solving Boost: provides training on problem solving skills to analyze the facts of a situation so that accurate conclusions are made (e.g. calculating a restaurant bill). This boost includes logical reasoning games such as *By the Rules*, based on the Wisconsin Card Sorting Test, arithmetic, and quantitative reasoning.

Comparison Group: Persons who are randomly assigned to the usual care comparison group will receive their usual care and a referral to "MyBrainGames", available for free at

MultipleScerosis.com. The games (Shopping List, Word Connect and Round Up) were launched in 2009 by the MS Technology collaborative and challenge the player's processing speed, working memory attention and task switching ability. We will not prescribe any specific amount of practice and participants will be asked to keep a log of any practice time– our preliminary studies have shown that self-report logs are significantly correlated (r=.96) to electronic monitoring logs. Participants will receive a weekly phone call to maintain their connection to the study but no other interventions. The comparison group will be asked to complete all data collection on the same schedule as the intervention participants and offered the printed intervention materials after the study.

Data Analysis: Inferential analysis will be used to test the study hypotheses. Data analyses will be conducted using SPSS.. Neuropsychological data will be scored by the testers and verified by a second staff member. Data will be entered and checked for accuracy. Internal consistency reliability coefficients for all self-report measures will be assessed with an expectation of alpha = .80 or above. Descriptive analyses will be used to obtain a profile of the sample. The groups will be compared at baseline on demographic and disease variables. Preliminary analysis for tests of assumptions such as normality, independence of errors, homogeneity of variance, and outliers will be conducted to determine if data transformations are necessary.

Missing data are often problematic for randomized controlled trials and various strategies are often used to manage missing data. We will use intention-to-treat strategies to handle missing data. More specifically, a "last observation carried forward" (LOCF) strategy in which missing data points are imputed based on the participant's existing data.

To account for cohort and city effects, multi-level analyses using SAS Proc Mixed will be conducted and any major effects observed will be included in subsequent analyses. A repeated measures (RM-ANOVA) design will be used to determine time and time by group effects on performance and self-report outcomes. Because of the large variability expected in a community-residing sample of persons with MS, we will use Analysis of Covariance (ANCOVA) to control for the differences among participants that are not germane to assessing the magnitude of the difference attributable to the treatment. Therefore, ANCOVAs will be performed to determine the differences between the intervention group and comparison groups at T2, T3, and T4, after controlling for baseline scores. Separate analyses will be conducted for each outcome measure.