DETAILED PROTOCOL

Title:
The Brain Health Champion study: Promoting non-pharmacological interventions in cognitive disorders

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Study Sponsor:
The Alzheimer Innovation Fund at Brigham and Women’s Hospital, Vettel Family Anne Romney Center for Neurologic Diseases

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**I. BACKGROUND AND SIGNIFICANCE**

Despite ongoing efforts for improvement, health care for persons with cognitive disorders and those at-risk remains inconsistent, often suboptimal, and largely unplanned (Odenheimer, 2013). Providing optimal care for patients with these conditions is challenging and critically important, given the myriad benefits that optimal care provides for patients and their families and for the health care system as a whole. For example, the estimated, total cost of health care, including long term care and hospice care, for Alzheimer disease (AD) in the United States alone was $236 billion dollars in 2016, close to 10% of all health care expenditures (Alzheimer Facts and Figures, 2016).

There have been several initiatives to identify what interventions constitute “optimal care” for patients with dementia. An effort led by the American Academy of Neurology (AAN) and the American Medical Association-convened Physician Consortium for Performance Improvement (PCPI), identified a set of 10 dementia care quality measures, derived from expert consensus, that providers and health systems should strive to achieve for these patients (Odenheimer 2013).

One of these measures, entitled “Caregiver Education and Support”, encourages the education of patients and caregivers on aspects of disease management, with a focus on promoting health behavior changes and referral to additional resources to achieve these changes.

Meeting this particular measure of quality dementia comprehensively is challenging. While it is simple for providers to introduce the importance of certain health behavior changes at an initial visit, and then reinforce recommendations every 3-6 months in longitudinal follow-up, this treatment plan often does not lead to sustained behavior changes.

Providing the care and treatment plan that is probably needed for many patients to make long-term changes is hindered by a number of factors. Structural factors include an overall health system which dis-incentivizes clinicians from carrying out regular, “face-to-face” or electronic encounters with these medically complex patients. These encounters are critical to re-enforce education and to successfully promote adoption and long-term maintenance of brain healthy behaviors. Institutional barriers include the fact that many hospitals or individual clinics employ clinicians who have inadequate professional time or training/skill-sets in the domain of motivating for behavior change. Finally, disease-specific factors include a high prevalence of neuropsychiatric symptoms among patients, including apathy and depression, and high rates of caregiver “burnout” and health problems, all of which directly impact patient behavior.

Clinical research has provided an abundance of evidence that even short-term adherence (6-months or less) to regimens of aerobic exercise, socially and mentally stimulating activities, and a “brain healthy” diet improves various health and quality-of-

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life outcomes for patients with cognitive disorders and their caregivers (Sobol, 2016; Dannhauser, 2015). And relevant to individuals with subjective cognitive changes, who are at-risk but do not have underlying disease, there is ample evidence that regular physical activity, among other activities, decreases the incidence of AD and improves overall cognitive functioning (Beckett, 2015; Smith 2016).

The benefits of tele-health and e-health programs, as well as motivational “booster” sessions to reinforce education and recommendations, have become increasingly recognized in different practice settings. Recent reviews support that notion. For example, tele-health delivered interventions for physical activity and dietary behavior change are successful in promoting short- and long-term behavioral changes (Goode, 2012).

For neurocognitive disorders, many of these programs have focused on psychosocial education for caregivers, which includes strategies to help patients maintain autonomy in daily activities and to meet patients’ and caregivers’ complex needs. For example, a recent tele-health program for caregivers employed a 14-week behavioral intervention using video instructional materials, workbook and telephone coaching in behavioral management, “pleasant events” scheduling, and relaxation (Steffen et al, 2016).

Fewer studies have primarily focused on patient adoption and maintenance of the evidence-based brain healthy behaviors which is the primary aim of the Brain Health Champions (BHC) program. One study engaged patients with MCI in a complex intervention for 12 weeks, including physical activity, group-based cognitive stimulation, and individual cognitive stimulation, and showed notable treatment effects in aspects of cognition, physical health (e.g., blood pressure, BMI), and fitness level (Dannhauser 2014). There is a clear need to improve the adherence to evidence-based brain healthy recommendations among patients with dementia and those at risk.

Finally, important to this proposed study, though these programs are not yet common in dementia care settings, there is strong evidence of interest from patients and their caregivers to participate in programs like BHC (Dal Bello Has et al, 2014).

II. SPECIFIC AIMS

The overall objective of this research is to investigate what clinical programs may be best for the delivery of optimal dementia care at the BWH Alzheimer Center. This particular study is designed to adapt the evidence-supported practice of employing frequent encounters in-between clinic visits, which has been effective in other diseases, to dementia care. The practice has been developed in to a clinical care program we have called the Brain Health Champion (BHC) program.

Adoption and maintenance of brain healthy behaviors is one of several, consensus-driven measures which, when met, can have a meaningful impact on quality of life and
the burdens of disease (Odenheimer 2013).

Our hypothesis is that patients who engage in frequent, motivational encounters between a clinician at the Alzheimer Center treatment team for 6 months, whether by telephone, video, or e-correspondence, and in-person visits (i.e., BHC), will lead to a 25% greater change in participation in brain healthy activities compared to patients receiving current clinical care (i.e., standard of care, or SOC).

These are more specific aims of the research:

1) To investigate whether augmenting the current clinical care in an academic, cognitive neurology center with a health behavior intervention will improve patient adoption and maintenance of treatment recommendations.
2) To investigate whether such a care program might improve other health outcomes, including: patients’ cognitive performance, sleep, daily functioning, quality of life measures, the utilization of health services and aspects of neuropsychiatric health.
3) To measure whether additional, motivational “booster sessions”, for 6 months following the 6-month study period, improve maintenance of brain health behavior changes made during the intervention period.

III. SUBJECT SELECTION

We aim to have 60 subjects complete the study.

Inclusion criteria:
1. Be age 50 to 95
2. Be an established patient at the Alzheimer Center at BWH, in that one has seen a behavioral neurologist at the Center at least once, with a plan for longitudinal neurologic care in the Center
3. Have a diagnosis of Subjective Cognitive Disorder (SCD) with an (MMSE guideline 27-30), Mild Cognitive Impairment (MCI) due to Alzheimer disease (AD), cerebrovascular disease (CVD), or mixed-type AD/CVD with an (MMSE guideline) 24-30, or mild dementia due to AD, CVD, or mixed-AD/CVD with an (MMSE guideline 20-30). In some cases, based on the clinical judgment of the treating neurologist, we may enroll a patient who falls outside of these guidelines or whose diagnosis and overall level of functioning does not perfectly correlate to their MMSE score.
4. Be sufficiently fluent in the English language to understand instructions and perform the cognitive and functional tests
5. Be able to travel to BWH for monthly follow up visits with the BHC study team.

Exclusion criteria:
1. Be enrolled in another health behavior or non-pharmacologic intervention for a neurocognitive disorder
2. Be unable to or unwilling to carry out regular physical exercise, multiple times weekly.

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3. Be not recommended to participate by their Internist/Primary Care Provider due to health-related concerns.

Clinicians at the BWH Alzheimer Center will identify appropriate participants in the course of their routine care. Attributes of an appropriate candidate will include: an identified need to improve their current brain healthy practices based on clinical interviews, and, their likelihood of completing the program (i.e. having minimal geographic barriers preventing regular in-person visits or other encounters). Ideally, patients will be identified prior to an upcoming, routine follow-up appointment. The study will be presented to possible participants as an investigation of different models of care in delivering brain health behavior recommendations.

All patients will receive the existing standard of care through the Alzheimer Center. The standard of care (SOC) includes, but is not limited to, management of appropriate medications, education about evidence-based, non-pharmacologic behavioral interventions, counseling on caregiver behavioral and support strategies, and referrals to social workers and other providers, if warranted.

It is likely that family members or other caregivers will play an active role in the study, especially for subjects who are at later stages of MCI due to AD and mild AD dementia. In every case, the clinical team will assess a new subject’s executive and decision-making capacity to understand and carry out the study on his/her own. If the clinical team is comfortable with the subject’s capacity to do so, then the involvement of a caregiver is not required. The clinical team will also recommend the involvement of a study partner at any time through the course of the study when and if they discern a decline of capacity for the subject to continue alone.

IV. SUBJECT ENROLLMENT

Potential subjects with a diagnosis of SCD, MCI due to AD, or mild AD dementia, who are established patients at the Alzheimer Center at BWH, and who meet the study’s criteria (section III, above), will be identified by their treating neurologist as appropriate candidates. The study team will aim to identify subjects ahead of a routine follow-up appointment; however, consideration for the study may happen during the appointment as well. If identified before, the study team will send potential subjects a letter (“BHC Prescreening Letter”, submitted) introducing them to the study basics and their possibility of enrollment. This letter will then be followed by a phone call from the study team to gauge participant interest, and will allow for planning of the in-person informed consent process. If there is a question of eligibility, the study team will conduct the screening phone call prior to offering participation via a recruitment letter.

At the follow-up appointment, the informed consent process will occur after the clinician has completed his/her usual SOC for the patient and their condition. In cases where time does not allow for consenting and enrollment at the follow-up, interested patients
will be offered a separate appointment with the study staff to complete the enrollment procedures. It is not feasible or necessary to allow for the typical, recommended time of 12 hours following informed consent to enroll subjects in this study for two reasons: 1) The study is designed to examine a direct extension of clinical care and a separate, research-dedicated visit to re-review the study procedures is not feasible within the Center's clinical infrastructure, and, 2) the procedures of the intervention arm pose very minimal risk, and the clinical team is well-poised to determine their established patient/partner's level of comprehension of the study during the visit. In addition, in most cases, participants have been contacted prior to the informed consent discussion by a letter and telephone call, which will allow time for additional consideration.

Following the informed consent, subjects will be randomized in REDCap to either the standard of care (SOC) arm or the Brain Health Champion (BHC) treatment arm. The randomization schedule in REDCap is hidden from investigators, and was randomly generated in Stata 14.0 as a 1:1 allocation stratified by diagnosis (SCD, MCI or dementia), using random block sizes of 2 and 4.

After target enrollment has been reached, we will assign additional participants to the BHC and SOC arm as needed to replace participants who have withdrawn from the study (were unwilling or unable to complete the protocol), matching based on diagnosis of SCD, MCI or mild dementia. We will use a separate informed consent to enroll patients who will assigned rather than randomized.

The treating physician, who has an established relationship with the patient and his/her caregiver, having seen them for at least one prior appointment at the Alzheimer Center, will decide whether the patient has capacity to consent alone or should be enrolled with a study partner. To aid in this decision regarding capacity, the treating clinician, who will be one of the study physicians, will consider the patient's MMSE/MoCA score, response to standard questionnaires, and clinical presentation. Consideration of capacity to make decisions and to understand treatment plans is an intrinsic aspect of routine clinical care at the Center.

As in other memory disorders studies, if there is any doubt after detailed consideration of existing data and clinical judgment, clinicians will use the submitted “BHC Capacity Assessment” questionnaire to establish whether patients have a comprehensive understanding of the research being described. The study will follow the PHRC preferred order of surrogates when enrolling a patient with a study partner.

The study team will be readily available to answer questions and discuss more details in the subsequent, weekly encounters, and will have a low threshold for withdrawing subjects if there if is any concern for patient safety or unwillingness to participate.

V.     STUDY PROCEDURES

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All in-person study visits will take place in a clinical exam room at the Center for Brain-Mind Medicine (CBMM), located in the Neurosciences Center on the 1st Floor of the Building for Transformative Medicine (BTM) or the Clinical Trials Hub at the Center for Clinical Investigation, on the 3rd floor of the BTM, part of Brigham and Women’s Hospital (BWH). The CBMM works closely with the BWH Alzheimer Center, which is part of the Ann Romney Center for Neurologic Diseases. The building is located at 60 Fenwood Road in Boston, Massachusetts, 02115.

Procedures (for all participants):

**Visit 1:** All subjects will be administered a general cognitive screen (either an MMSE, or, MoCA), unless one has been completed within 1 month prior to Visit 1. Caregivers, when determined necessary by the clinical team, will be administered a Neuropsychiatric Inventory-Questionnaire (NPI-Q; Kaufer 2000) and Activities of Daily Living Questionnaire (ADLQ; Johnson 2004). All subjects will also complete: a general survey querying their current cognitively/socially stimulating activities and experiences (a study-specific tool, which also embeds the Florida Cognitive Activities Scale (FCAS) within; Schinka 2005), a physical activity survey (IPAQ-L; Craig 2003), a questionnaire addressing current mood (Geriatric Outcomes Sleep-Study Scale; Hays 1992), a dietary intake questionnaire (Mediterranean Score; Goulet 2003), a survey which reveals social network size (Social Network Index; Cohen 1997) and degree of social connectedness (Social Connectedness and Social Assurance Scale; Lee 1995), and a survey that queries overall quality of life (Flanagan Quality of Life Scale; Burckhardt 2003).

The BHC program arm, procedures:

**Visit 1:** (Second part of Visit 1) Following consent and randomization by the clinician and the BHC, the team will review logistical details about the weekly encounters and monthly in-person visits with the BHC. Using self-report data provided on the questionnaires, and guided by population-based recommendations, the team will create personalized goals with the subject in each major brain health domain (exercise, diet, social/cognitive stimulation) and record them on the “BHC Goals Form” (submitted). Verbal contract on next steps for behavior change will then occur, in advance of Visit 2. The team will establish subject/caregiver’s preference for use of either: a) email, b) phone contact, c) video conference, or some combination, for the once weekly, 15-minute BHC interactions.

**Weekly encounters:** 1, 2, 3, 4, 5 (Weeks 1-5): 15-minute motivational interview
sessions between BHC and subject/caregiver. Content will include discussion of progress and challenges of meeting the personalized goals. The BHC will record/track progress and challenges toward goals in brief, clinical progress notes in the electronic medical record (EMR). Communication between the patient and the BHC will occur over phone, Partners Skype for Business, Partners Send Secure, and/or Partners Patient Gateway.

**Visit 2:** (Week 6, +/- 1 week): 30-minute visit to involve *Brain Health Champion* and *subject/caregivers*. Champion will employ motivational interviewing concepts and style, review of last 5 weeks of brain health activities, identify barriers to achieving goals, and prepare written/verbal short-term goals with subject in advance of Visit 3.

**Weekly encounters:** 6, 7, 8, 9, 10 (Weeks 7-11): 15-minute motivational interview sessions between *BHC* and *subject/caregiver*. Content will include discussion of progress and challenges of meeting the personalized goals. The BHC will record/track progress and challenges toward goals in brief, clinical progress notes in the electronic medical record (EMR).

**Visit 3:** (Occurs whenever the next, usual follow-up visit is for longitudinal care by the clinician; any time from Week 12 to Week 24): Standard neurology follow-up visit, to involve *patient, Brain Health Champion (BHC)*, and *treating clinician*. This visit will involve typical, standard of care (SOC) treatment, including medication management, cognitive/neuropsychiatric assessment, and referral to other providers or social workers, if needed. There will be ongoing discussion/promotion of brain health activities. BHC will execute verbal or written contract of brain health goals in advance of Visit 4.

**Weekly encounters:** 11, 12, 13, 14, 15 (Weeks 13-17): 15-minute motivational interview sessions between *BHC* and *subject/caregiver*. Content will include discussion of progress and challenges of meeting the personalized goals. The BHC will record/track progress and challenges toward goals in brief, clinical progress notes in the electronic medical record (EMR).

**Visit 4:** (Week 18, +/- 1 week): 30-minute visit to involve *Brain Health Champion* and *subject/caregivers*. Champion will employ motivational interviewing concepts and style, review of last 5 weeks of brain health activities, identify barriers to achieving goals, and prepare written/verbal short-term goals with subject in advance of Visit 5.

**Weekly encounters:** 16, 17, 18, 19, 20 (Weeks 19-23): 15-minute motivational interview sessions between *BHC* and *subject/caregiver*. Content will include discussion of progress and challenges of meeting the personalized goals. The BHC will record/track progress and challenges toward goals in brief, clinical
progress notes in the electronic medical record (EMR).

**Visit 5:** (Occurs whenever the next, usual follow-up visit is for longitudinal care by the clinician; any time from Week 12 to Week 24, or later): Standard neurology follow-up visit, to involve patient, Brain Health Champion, and treating clinician. This visit will involve typical, standard of care (SOC) treatment, including medication management, cognitive/neuropsychiatric assessment, and referral to other providers or social workers, if needed. All subjects/caregivers will then repeat all of the study questionnaires/surveys (see Visit 1, above). At the end of the visit, participants who consent will be randomized to receive either biweekly 15-minute “booster” phone calls, or no additional contact with the study team.

**Biweekly “booster” encounters (for subjects randomized to receive them):**
15-minute motivational interview sessions between BHC and subject/caregiver. Content will include assessing maintenance of brain health behavioral changes, identifying challenges to maintaining brain health changes, and brainstorming solutions to improve adherence to goals and recommendations.

**Additional data collection, 3 and 6 months after Visit 5:** 30-minute visit between BHC and patient/caregivers. The study team will also re-administer the dietary intake questionnaire (Mediterranean Score; Goulet 2003), the general survey on current cognitively/socially stimulating activities (a study-specific tool, which also embeds the Florida Cognitive Activities Scale (FCAS) within; Schinka 2005), and the physical activity survey (IPAQ-L; Craig 2003). At the 6-month post-study visit, BHC will also elicit feedback regarding the program and perceived benefits for health.

**The standard of care (SOC) arm, procedures (following Visit 1):**

**Visit 2:** (Occurs whenever the next, usual follow-up visit is for longitudinal care by the clinician; any time from Week 12 to Week 24): Standard neurology follow-up visit, to involve patient, Brain Health Champion, and treating clinician. This visit will involve typical, standard of care (SOC) treatment, including medication management, cognitive/neuropsychiatric assessment, and referral to other providers or social workers, if needed. All subjects/caregivers will then repeat all of the study questionnaires/surveys (see Visit 1, above).

**Visit 3:** (Occurs whenever the next, usual follow-up visit is for longitudinal care by the clinician; any time from Week 12 to Week 24, or later):

Visit will involve patient (+/- caregiver, if relevant) and treating clinician. This
visit will be the typical, standard of care (SOC) treatment, including medication management, general counseling on brain health activities, cognitive and neuropsychiatric assessment, and referral to other providers or Social Work, if needed. All subjects/caregivers will then repeat all of the study questionnaires/surveys (see Visit 1, above).

**End-of-Study Encounter, 3-months after Visit 3:** 30-minute visit between a clinical team member and subject/caregiver. The team member will elicit feedback regarding the program and perceived benefits for health. The team member will re-administer the dietary intake questionnaire (Mediterranean Score; Goulet 2003), the general survey on current cognitively/socially stimulating activities (a study-specific tool, which also embeds the Florida Cognitive Activities Scale [FCAS] within; Schinka 2005), and the physical activity survey (IPAQ-L; Craig 2003).

As is discussed in the informed consent form, all participants may be contacted 1 year or more following the end-of-the study to for additional feedback and to complete additional questionnaires, if willing.

Subjects’ basic demographic and health information, as well as the study team’s notes from all of the study encounters, will be recorded in an off-line, study database, which is protected by Partners Health Care IT security.

**VI. BIOSTATISTICAL ANALYSIS**

The study endpoint in this 6-month, open-label, randomized controlled trial is the absolute change or percent change of participants’ brain healthy activities, as measured by three questionnaires/scales: the Mediterranean Score, the IPAQ-L, and a survey on cognitively/socially stimulating activities and experiences (see Procedures, above, for references related to these instruments).

We will mainly use multivariate analysis of covariance (MANCOVA) methods to compare the Brain Health Champion (BHC) program intervention to the standard of care (SOC). We will attempt to control for various background factors, such as the severity of cognitive deficits within each disease condition (i.e., there is a range of cognitive functioning for those included the diagnosis of Mild Cognitive Impairment), and variations in the delivery of care between different physicians.

In addition to the main analysis, we will also analyze changes from baseline in various measures for the two conditions, including: overall cognitive function (MMSE, MoCA), neuropsychiatric status (NPI-Q), sleep behavior and quality of sleep (MOS-SS), daily functioning (ADLS), Geriatric Depression Scale (GDS), and overall quality of life in neurologic patients (Flanagan QOL scale). We will also perform separate analyses for closer investigation of how age and the involvement of a caregiver/study partner may modify the experimental effects. In the intervention (BHC) group, we will investigate the
effect of monthly “booster” sessions on subjects’ maintenance of brain healthy changes after the 6-month study period, compared to BHC subjects who receive no additional contact from the study team.

A power analysis is not applicable here. This proof-of-concept, controlled pilot study will not have an adequate sample size to yield any reasonable degree of statistical power from the results.

VII. RISKS AND DISCOMFORTS

Physical Exercise

This study is a clinical treatment program that includes the continued, weekly recommendations for subjects to carry out physical exercise. The type of aerobic, physical activity that is recommended, and that is beneficial for brain health, requires that subjects have some modicum level of cardio-pulmonary fitness. The treating clinician who is selecting possible subjects will screen for this level of fitness in the course of the initial neuro-medical evaluation of the subject, and the Brain Health Champion will regularly monitor subjects’ tolerance to the recommended physical exercise through the study course, with regular feedback to the clinician. Subjects or caregivers/partners who report that the exercise recommendations are too difficult or deleterious to health in any way will immediately be advised to reduce or cease their efforts.

In order to screen for any medical or psychological concerns which would impede subjects’ study participation, either because of exercise intolerance or suspected intolerance to repeat cognitive testing, the treating clinician/investigator will also contact all subjects’ PCPs, prior to study commencement, by clinical messaging or telephone.

Weekly Study Encounters

A member of the study team (the BHC) will initiate weekly encounters with subjects/partners by video, telephone, or e-correspondence. Subjects may become frustrated by this weekly contact. They will be encouraged from the start of the study to express concerns to the study team about their psychological well-being, in relationship to the frequency of this contact, through the course of the study.

Repeated cognitive, functional, and neuropsychiatric testing

This study requires subjects to complete various health questionnaires and perform basic cognitive and behavioral tasks at several time points throughout the course. Subjects may become anxious, tired, or frustrated with these tasks. The study team is well trained in the administration of these instruments and will attempt to make subjects as comfortable as possible. Subjects and partners can take a break or discontinue the testing at any time.

VIII. Potential Benefits
Study participants and their caregivers/partners will have the chance to personally benefit from increased adherence to current, evidence-based recommendations for brain healthy behaviors. However, there are no proven benefits to participating in this study.

More globally, the results of this study will inform the current, clinical treatment of patients with subjective cognitive complaints and with cognitive disorders at the BWH Alzheimer Center.

IX. MONITORING AND QUALITY ASSURANCE

The Principal Investigator will report any and all serious and non-serious adverse events to the Partners IRB within a timely manner. Study personnel must immediately report to the PI any adverse events from this study. All adverse events will be reviewed by the PI and reported to the Partners Human Research Committee (HRC) in accordance with ICH Guidelines. The PI will maintain a tracking log to reflect all adverse events regardless of relationship or expectedness and submit the updated log each year during the IRB renewal process.

The PI will be responsible for monitoring and assuring the validity and integrity of all of the data, for monitoring the day-to-day activities of all study procedures, and for the adherence to the IRB-approved protocol.

X. REFERENCES


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