DETAILED PROTOCOL

NCT Number:
NCT03772977

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

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

Study Principal Investigator:
Seth A. Gale, M.D.

Co-Principal Investigator:
Kirk R. Daffner, M.D.

Co-Investigators:
Diler Acar, M.D.
Taylor Krivanek, B.A.
Brittany McFeeley, B.S.
Casey Nicastri, B.S.
Scott McGinnis, M.D.
Kim Willment, Ph.D.

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 care 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. Importantly, there are no such care quality measures for patients who are cognitively normal but at-risk for dementia.

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-life outcomes for patients with cognitive disorders and their caregivers (Sobol, 2016; Dannhauser, 2015). In addition, for cognitively normal individuals with risk factors for dementia and individuals with subjective cognitive complaints (who do not yet have the underlying disease), there is ample evidence that participation in brain healthy behaviors decreases the incidence of dementia and improves overall cognitive functioning, quality of life, and other outcomes (Beckett, 2015; Ngandu et al., 2015; Okereke et al., 2012; Smith 2016; Wilson et al., 2002).

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 and dementia risk reduction at the BWH Alzheimer Center and BWH primary care centers. 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 or virtual 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., physician counseling and education, or PCE).

These are more specific aims of the research:

1) To investigate whether augmenting the current clinical care in an academic, cognitive neurology center or primary care 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 investigate the feasibility, ease of use, and benefit for behavior change of the employed mobile health platforms, Fruit Street, Fitbit, and MealLogger Pro.
4) To measure whether additional, motivational "booster sessions", for 6 months following the 6-month intervention, improve maintenance of brain health behavior changes made during the intervention period.

III. SUBJECT SELECTION

We aim to have 85 subjects complete the study.

A. Overall enrollment criteria:

Inclusion:

All participants:

1) Age 60-79
2) Existing patient at Brigham Health system with at least one prior visit with providers and plans to establish/continue longitudinal care
3) Proficiency in English
4) In adequate physical health, as determined by participant's physician-provider, to safely complete participate the physical exercise encouraged by the study
5) Willing to complete all study-related activities for 12 months
6) Willing to be randomized to either lifestyle intervention group
7) Willing and able to travel to the Brigham and Women's Hospital (Boston) regularly OR
   Access to a smartphone and/or computer with webcam and stable internet access

Neurology participants:

1) Have a diagnosis of 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, patients who score outside of these guidelines on the MMSE may be enrolled, as diagnosis does not always correlate to MMSE score
2) Telephone Interview for Cognitive Status (TICS-40) greater than 20
3) A reliable study partner (in subjects with mild dementia, this will be the caregiver) needs to be identified who can complete questionnaires every 6 months about participant's cognition/daily functioning, and, communicate regularly with study personnel about participant's activities, health, and safety

Primary Care "At risk" participants:

1) Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) dementia risk score of ≥ 6, or score of 5 *plus* one of the following: a history of ADRD in a first-degree relative, or type II diabetes or "pre-diabetes" spectrum (A1C level ≥ 5.7)
2) Telephone Interview for Cognitive Status (TICS)-40 greater than 31
3) AD8 score less than or equal to 2
4) A reliable study partner (e.g. family member) needs to be identified who can complete questionnaires every 6 months about participant's cognition/daily functioning

Exclusion:

All participants:

1) Current levels of aerobic physical activity that cause sweating or breathlessness at least twice a week, lasting 20-30 minutes (consistent with "high" physical activity level, per the CAIDE risk score)
2) Score greater than or equal to 2 standard deviations below age- and education-adjusted norms on two or more tests in the cognitive battery (PACC-BHC)

3) Current significant or unstable medical, neurologic or psychiatric illness, that impairs mobility, mild to moderate aerobic exercise capacity, or daily functioning
4) Significant cardiovascular disease (including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, or uncontrolled angina)
5) Serious conduction disorder (e.g., 3rd degree heart block) or uncontrolled arrhythmia
6) Myocardial infarction, major heart surgery (i.e., valve replacement, bypass surgery, stent placement, angioplasty), deep vein thrombosis, or pulmonary embolus in the past 6 months
7) Lung disease requiring either regular use of corticosteroids or the use of supplemental oxygen (inhaled steroids for asthma is permissible)
8) Significant neurologic disease, including any form of Parkinson disease, Huntington disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma with persistent neurologic sequelae or known structural brain abnormalities
9) Large vessel stroke in the past 2 years
10) History of TIA or small vessel stroke in the last 6 months
11) History of alcohol or substance abuse or dependence within the past 2 years, as per DSM-5 criteria
12) Geriatric Depression Score (GDS) ≥ 10, unless deemed by treating provider *not* to have active depression (e.g. adjustment disorder, grief reaction)
13) Concerns of the participating PCP or neurologist about health risks for subject participation, or, if a subject is physically unable to carry out recommendations
14) Resides in an assisted living facility or nursing home
15) Life expectancy of < 2 years
16) Current participation in a pharmacological or other interventional AD trial

The PI (Dr. Gale), in consultation with participating providers, will have ultimate discretion regarding including or excluding participants based on clinical factors.

All patients will receive physician counseling and education (PCE) through the Alzheimer Center or primary care center. PCE 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. For subjects who enroll without the daily involvement of a caregiver, the clinical team may require the involvement of such a person, at any time through the course of the study, if they identify a decline in the participant's capacity to

safely and optimally carry out the study procedures on their own.

B. Subject selection, **Step 1**: Electronic medical record (EMR) search

The first step in subject selection will be a strategic search of the EMR conducted by study personnel. All potential subjects will be age 60-79, will be established patients of the Brigham Health system, and ideally will have indicated interest in participation in research through registration or intake to their clinic. Treating neurologists will identify possible neurology participants during their clinical interviews, either prior to or during a routine follow-up appointment or during that appointment. To screen for potential primary care "At-risk" participants, medical records of patients with upcoming appointments in Brigham Primary Care will be screened using EPIC research reports, extracting the following data: last blood pressure (systolic BP >140), body-mass index (BMI >30 kg/m2), last A1C level (A1C level ≥ 5.7), and total serum cholesterol (cholesterol >250 mg/dl). These conditions are part of the calculation of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score (see details, below) (Kivipelto et al., 2006).

After running the research report, records will be manually screened for family history of ADRDs or exclusionary medical conditions. Primary care patients with at least *one* of these risk factors will be eligible for further screening, by telephone (see below). After identifying potential participants for telephone screening, personnel will communicate with individuals' primary providers to determine if they can safely participate, considering any physical limitations and other medical/psychosocial concerns.

C. Subject selection, **Step 2**: Letter and telephone screening

If providers concur that selected participants are eligible for the study, study personnel with send a letter *("BHC Prescreening Letter, At-Risk",* submitted) electronically (by the Gateway portal) and by mail, to patients, and follow-up with a screening telephone call to gauge interest in research (see "*Telephone Script, At-Risk"*).

For potential neurology participants: During phone screens, personnel will introduce the study, gauge interest, inquire about a reliable study partner to complete functional assessment questionnaires and support participant behavior change during the trial, and assess the current amount of physical activity. Engagement in aerobic activity ≥2 times per week, lasting at least 20-30 minutes will be considered a "high" exercise level and be exclusionary. If these criteria are met, personnel will then administer the Telephone Interview for Cognitive Status (TICS)-40, an 11-question validated tool with a maximum score of 40. Potential neurology participants must score ≥20.

For potential primary care participants: During phone screens, personnel will introduce the study, gauge interest, and inquire about the availability of a person (e.g. family member) who can periodically complete functional assessment questionnaires over the two-year trial. Personnel will also assess educational attainment, and physical activity level, which are not generally available in the EMR, to calculate CAIDE dementia risk score. The CAIDE score ranges from 0 to 15, and accounts for age, sex, blood pressure, BMI, educational attainment, cholesterol level, and degree of physical activity. Because all participants in the study will be at least 60 years old, they will start with a CAIDE score of 4. Consistent with CAIDE, engagement in aerobic activity ≥2 times per week, lasting at least 20-30 minutes will be considered a "high" exercise level and be exclusionary. Eligible participants must have a CAIDE score of ≥ 6 or a CAIDE score of 5 *plus* one of the following: a history of ADRD in a first-degree relative or, type II diabetes or "pre-diabetes" spectrum (A1C level ≥ 5.7) (CAIDE+).

If CAIDE+ criteria are met, personnel will administer the (TICS)-40 and AD8, an 8-point scale for detecting functional abilities. Potential at-risk participants will be eligible if they score ≥31 on the TICS and ≤ 2 on the AD8, indicating well-preserved functioning in activities of daily living. An additional level of screening will occur during baseline assessments: If participants score ≥2 standard deviations below age- and education-adjusted norms on two or more tests in the cognitive battery, they will be excluded. If at-risk patients score worse than the cut-off values on the phone screen (TICs or AD8), or on the in-person neuropsychological tests, their PCPs will be informed, allowing them to determine if further clinical evaluation is warranted.

All eligible participants: If eligible, personnel will schedule an in-person enrollment visit with the participant and study partner (if applicable) on the day of their next provider appointment.

When an in-person visit is not possible, personnel will schedule a virtual enrollment visit on Enterprise Zoom with the participant and study partner. If possible, this visit will take place on the day of their next provider appointment. Instructions for accessing Zoom will be sent to the participant via their preferred contact method (i.e., Gateway, secure email, or unencrypted email). If potential participants prefer to correspond via unencrypted email, study personnel will gain verbal consent during the phone screen (see Telephone Script). Prior to virtual enrollment visits, the Informed Consent Form will be sent electronically for participants to review via REDCap survey link.

IV. SUBJECT ENROLLMENT

At the follow-up appointment, the informed consent process will occur after the clinician has completed his/her usual PCE 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.

When in-person visits are not possible, all consent procedures will occur electronically. At the beginning of the virtual visit, study staff will conduct the consenting discussion. The participant will sign the consent form in REDCap using Partners REDCap e-Consenting tool.

Following the informed consent, subjects will be randomized in REDCap to either the physician counseling and education (PCE) or the Brain Health Champion (BHC) treatment arm. The randomization schedule in REDCap is hidden from investigators and was randomly generated in Excel as a 1:1 allocation. Randomization is stratified by diagnosis (MCI or at-risk), using block sizes of 4. Informed consents forms can be either mailed or emailed via REDCap link (with verbal consent for unencrypted email obtained during telephone screening) to participants, to review prior to visits and to e-sign following the screening visit, if desired.

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

For cognitively impaired participants, the treating neurologist, 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 caregiver. 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 caregiver.

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

Baseline, 6-month, and 12-month in-person study visits will start either at the Phyllis Jen Center for Primary Care (PJC), at Brigham and Women's Hospital (BWH), at 45 Francis Street, Boston, MA 02115, or at the Center for Brain/Mind Medicine (CBMM), located in the Neurosciences Center on the 1st Floor of the Building for Transformative Medicine (BTM). The building is located at 60 Fenwood Road in Boston, Massachusetts, 02115. Assessments will take place at the Clinical Trials Center or at the Clinical Trials Hub, at 45 Francis Street or 60 Fenwood Road respectively, both at the Center for Clinical Investigation, part of Brigham and Women's Hospital (BWH).

When in-person visits are not possible, baseline, 6-month, and 12-month visits will occur virtually on Enterprise Zoom, following MGB requirements for Zoom use.

Procedures (for all participants):

Visit 1 (Part 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, and brief neuropsychological battery (PACC-BHC (Papp et al., 2017); which includes: 1) Free and Cued Selective Reminding Test (FCSRT); 2) Logical Memory, immediate and delayed Story Recall; 3) Visual Paired Associates; 4) Digit-Symbol Substitution Test; 5) Trail Making Test, Part A; 6) Trail Making, Part B; 7) Number Span, 8) Category Fluency (animals, fruits, vegetables); and 9) Phonemic Fluency. (See tests, submitted). Caregivers, when determined necessary by the clinical team, will also 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 demographic information questionnaire, 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 (PASE; Washburn 1993), a sedentary behavior survey (SIT-Q-7d survey; Wijndale 2014), a questionnaire addressing current mood (Geriatric Depression Scale; Gilley 1997), a general sleep survey (Medical 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), a survey that queries overall quality of life (Flanagan Quality of Life

Scale; Burckhardt 2003), and a survey measuring level of self-activation (PAM-13; Hibbard 2005). A questionnaire about observed changes in the subject's memory and daily functioning will be completed by the participant, and separately by a study partner identified at the start of the study ("informant") (CFI; Amariglio et al., 2015). Participants will have the option to complete questionnaires on paper or electronically via REDCap's survey feature. If Visit 1 is completed virtually, participants will be sent instructions for downloading the study mobile applications and setting up their Fitbit devices.

Photographed dietary intake: Subjects will photograph all food and drink intake using the "Food Log" photo function on the Fruit Street application (for BHC participants) or MealLogger Pro (for PCE participants) for a consecutive, 4-day period, including one weekend day, within two weeks of each assessment (Baseline, 6-month, and 12-month visits). The photographs will be analyzed by the study dietician to compare to self-reported diet on Mediterranean Score questionnaire. Additional details about MealLogger Pro are in *PCE arm procedures* (below).

Fitbit: All subjects will receive a Fitbit Inspire HR device, either at their in-person enrollment visit or by mail. Subjects will be instructed to wear the device for a consecutive, 4-day period, including one weekend day, within two weeks of each assessment (Baseline, 6-month, and 12-month visits). The data from the device, which is viewable by the team through the secure Fruit Street application, will be analyzed to compare to self-reported physical activity on the PASE questionnaire. Use of the Fitbit device between assessment periods will be encouraged but not required.

The BHC program arm, procedures:

Visit 1: (Part 2) Following consent and randomization by the clinician and the BHC, the team will review logistical details about the weekly encounters and monthly in-person or virtual visits with the BHC. Study personnel will introduce Fruit Street, a HIPAA-compliant mobile health application with video calling and two-way messaging feature, which has been well-established for diabetes prevention, and the Fitbit device and mobile application. Personnel will instruct subjects on how to download and navigate each of the applications, set up their Fitbit device, and sync the applications. Subjects will be assigned a deidentified username and password to log in to the applications. If participants do not own a smart phone, one will be provided by the study team for use during the study. Weekly 15-minute virtual interactions will occur within the Fruit Street application. The study team will establish preference for in-person or virtual

visits (within the Fruit Street application) at 6, 12, and 18 weeks. In-person visits will be encouraged, but not required. The team will also establish subject/caregiver's preference for use of either Gateway, email, or phone contact for study-related communications. If email is the preferred method of contact, study staff will determine the preference for send secure or unencrypted email, and unencrypted email consent will be obtained as necessary.

Weekly encounters: 1, 2, 3, 4, 5 (Weeks 1-5): 15-minute motivational interview sessions between BHC, subject, and caregiver (if applicable). 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 within Fruit Street, using either the website or the mobile application. Between weekly encounters, participants may communicate with the health coach regarding their progress, challenges, or questions via in-app messaging.

Visit 2: (Week 6, +/- 1 week): 60-minute visit (in person or virtual).

Part 1 (15 minutes) will involve subject, caregiver (if applicable) and BHC. The BHC will employ motivational interviewing and behavioral activation techniques to encourage healthy behaviors, review the 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.

Part 2 (45 minutes) will involve subject, BHC, caregiver (if applicable) and research dietician. The dietician will carry out individual nutritional counseling, which will involve: Detailed Mediterranean diet nutrition education (see "Brain Health and Diet" supplement), a structured review of current dietary intake, and personalized recommendations to improve adherence to the Mediterranean diet.

Weekly encounters: 6, 7, 8, 9, 10 (Weeks 7-11): 15-minute motivational interview sessions between BHC, subject, and caregiver (if applicable). 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). Between weekly encounters, participants may communicate with the health coach regarding their progress, challenges, or questions via in-app messaging.

Visit 3: (Week 12, +/- 1 week) 30-minute visit (in person or virtual) to involve BHC, subject, and caregiver (if applicable). BHC 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 4. When appropriate, this visit may be combined with a standard neurology or primary care follow-up visit, which would involve physician education and counseling, including medication management, cognitive/neuropsychiatric assessment, and referral to other providers or social workers, if needed.

Weekly encounters: 11, 12, 13, 14,15 (Weeks 13-17): 15-minute motivational interview sessions between BHC, subject, and caregiver (if applicable). 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). Between weekly encounters, participants may communicate with the health coach regarding their progress, challenges, or questions via in-app text messaging.

Visit 4: (Week 18, +/- 1 week): 30-minute visit (in person or virtual) to involve Brain Health Champion, subject, and caregiver (if applicable).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, subject, and caregiver (if applicable). 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). Between weekly encounters, participants may communicate with the health coach regarding their progress, challenges, or questions via in-app text messaging.

Visit 5: End-of-Intervention (6-month assessment; Week 24 +/- 1 week).

Part 1. 30-45 minutes. **Routine primary care or neurology follow-up visit**, involving subject, BHC, caregiver (if applicable) and treating provider. In this visit, the provider will address any current medical and health concerns and medication management, as per usual. BHCs will then provide a brief, overall assessment and summary of subjects' progress in achieving personalized brain health goals, and whether they met the threshold for consensus-driven, brain health activity guidelines in the 6-month intervention.

Part 2. 2 hours. **End-of-Intervention assessment.** Participants will complete all the assessments they completed at Visit 1/Part 1 (see above). In addition, they will complete general and health-coach/mobile

health specific feedback on the intervention. Participants will then be asked through a different informed consent process, if they are willing to be randomized to a 6-month "booster" study extension vs. having no additional contact with the study team.

Biweekly "booster" encounters (for subjects randomized to receive them): 15-minute motivational interview sessions between BHC, subject, and caregiver (if applicable). 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.

Visit 6: (1-year assessment [6-month post end-of-Intervention]); Weeks 50-52): 2 hours. Subjects and study partners will complete all the assessments they completed at Visit 1/Part 1 (see above).

Additional visits: If needed for any routine medical care, primary care visits will continue to occur during study enrollment, from baseline through Week 48. When possible, and as in the study design of a clinical team approach, BHCs will be present for these visits. After all medical concerns are addressed, BHCs will promote ongoing brain health behaviors for participants.

The Physician counseling and education (PCE) arm, procedures:

Visit 1: (Part 2) (Week 0) 15-20 minutes**.** Participating providers will review the essentials of brain-healthy behaviors, guided by an educational handout ("Brain Health Education Handout") which will be given to subjects. Physicians will lead a discussion about specific ways to optimize brain healthy behaviors. Study personnel with also introduce the Fitbit device and mobile application and MealLogger Pro, a mobile application used for photographing food intake, and will instruct subjects on how to download and navigate the applications and set up their Fitbit device. Subjects will be assigned a deidentified username and password to log in to the MealLogger Pro and Fitbit applications. If participants do not own a smart phone, one will be provided by the study team for use during the study. The team will also establish subject/caregiver's preference for use of either Gateway, email, or phone contact for study-related communications. If email is the preferred method of contact, study staff will determine the preference for send secure or unencrypted email, and unencrypted email consent will be obtained as necessary.

Visit 2: (6-month assessment; Week 24 +/- 1 week) 2 hours, 20 min

Part 1. 20 minutes. **A neurology or primary care follow-up visit** will occur at week 24, involving participant, caregiver (if applicable), and participating

provider. In this visit, the provider will address current medical and health concerns and medication management, as per usual. Physicians will then review the essentials of brain healthy behaviors with subjects and discuss the status of subjects' following through on brain health behavior recommendations introduced at Visit 1.

Part 2. 2 hours. **End-of-Intervention assessment.** Participants and study partners will complete all the assessments they completed at Visit 1/Part 1 (see above). In addition, they will complete general feedback on the intervention.

Every 6 weeks between Visit 1 and Visit 2 (Weeks 6, 12, and 18), PCPs will distribute educational handouts summarizing recommendations via the electronic patient portal and on paper, in order to reinforce the material taught at Visit 1.

Visit 3: (1-year assessment [6-month post end-of-Intervention]): 2 hours. Subjects and study partners will complete all the assessments they completed at Visit 1/Part 1 (see above).

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 PASE, 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 physician counseling and education (PCE). 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. We will complete both an intention to treat (ITT) analysis including all subjects and a subanalysis including only subjects who finished (did not drop out) of the study. Secondary analysis will look at the correlations between self-report physical activity (PASE) and FitBit step counts, and self-report Mediterranean diet adherence

and quatified/photographed dietary intake.

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), dementia risk score (CAIDE), sleep behavior and quality of sleep (MOS-SS), daily functioning (ADLS), patient activation (PAM-13), sedentary behavior (SIT-Q-7d), 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 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 intervention, 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.

Fruit Street Security

Fruit Street has implemented reasonable measures to protect the information that they collect and store (e.g. hashed user password and SSL encryption), taking into consideration the types of risks they face and the reasonable protections available to them. No method of protecting information is 100% secure, and they cannot guarantee its absolute security. Consequently, they cannot ensure or warrant the security of any information that participants transmit to them. Once Fruit Street receives participant data, they take steps to ensure security on their systems and/or on the systems of their service providers, but this is not a guarantee that such information may not be accessed, disclosed, altered, or destroyed by breach of such safeguards.

VIII. Potential Benefits

Study participants will have the chance to personally benefit from increased adherence to current, evidence-based recommendations for brain healthy behaviors. However, there are no proven health benefits to participating in this study.

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.

All participants can receive up to $300 compensation for participating in the study. Compensation will be split into three installments of $100, paid after the baseline assessment (0 months), end-of-intervention assessment (6 months), and end-of-study assessment (12 months). If participants are compliant with wearing their Fitbit device, they will get to keep it at the end of the study. If participants are not compliant, a pre-paid envelope will be mailed to their house so that they can return the device free of cost. In certain circumstances, when providing one's own transportation is a barrier to participation, study funds will cover the cost of transportation to in-person study visits.

Additionally, parking passes will be provided for all in-person study visits.

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

Amariglio RE, Donohue MC, Marshall GA, et al. Tracking early decline in cognitive function in older individuals at risk for Alzheimer disease dementia: the Alzheimer's Disease Cooperative Study Cognitive Function Instrument. JAMA Neurol 2015;**72**(4):446-54 doi: 10.1001/jamaneurol.2014.3375.

Beckett MW, Ardern CI, Rotondi MA. A meta-analysis of prospective studies on the role of physical activity and the prevention of Alzheimer's disease in older adults. BMC Geriatr. 2015 Feb 11;15:9. doi: 10.1186/s12877-015-0007-2. PubMed PMID: 25887627.

Burckhardt, C. S., Anderson, K. L., Archenholtz, B., & Hagg, O. (2003). The Flanagan Quality of Life Scale: Evidence of construct validity. Health and Quality of Life Outcomes, 1, 59. doi: 10.1186/1477-7525-1-59

Cohen S, Doyle WJ, Skoner DP, Rabin BS, Gwaltney JM Jr. Social ties and susceptibility to the common cold. JAMA. 1997 Jun 25;277(24):1940-4. PubMed PMID: 920063

Dal Bello-Haas VP, O'Connell ME, Morgan DG, Crossley M. Lessons learned: feasibility and acceptability of a telehealth-delivered exercise intervention for rural-dwelling individuals with dementia and their caregivers. Rural Remote Health. 2014;14(3):2715. PubMed PMID: 25081991

Dannhauser TM, Cleverley M, Whitfield TJ, Fletcher BC, Stevens T, Walker Z. A complex multimodal activity intervention to reduce the risk of dementia in mild cognitive impairment--ThinkingFit: pilot and feasibility study for a randomized controlled trial.

BMC Psychiatry. 2014 May 5;14:129. doi: 10.1186/1471-244X-14-129. PubMed PMID: 24886353

Gilley DW, Wilson RS. Criterion-related validity of the Geriatric Depression Scale in Alzheimer's disease. J Clin Exp Neuropsychol. 1997 Aug;19(4):489-99. PubMed PMID: 9342685

Goode AD, Reeves MM, Eakin EG. Telephone-delivered interventions for physical activity and dietary behavior change: an updated systematic review. Am J Prev Med. 2012 Jan;42(1):81-8. doi: 10.1016/j.amepre.2011.08.025. Review. PubMed PMID: 22176852.

Hays, R. D., & Stewart, A. L. (1992). Sleep measures. In A. L. Stewart & J. E. Ware (eds.), Measuring functioning and well-being: The Medical Outcomes Study approach (pp. 235-259), Durham, NC: Duke University Press.

Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM; ERICCA Trial Investigators.. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. N Engl J Med. 2015 Oct 8;373(15):1408-17. doi: 10.1056/NEJMoa1413534. PMID: 26436207

Hibbard JH, Mahoney ER, Stockard J, Tusler M. Development and testing of a short form of the patient activation measure. Health Serv Res. 2005 Dec;40(6 Pt 1):1918-30. PMID: 16336556

Johnson N, Barion A, Rademaker A, Rehkemper G, Weintraub S. The Activities of Daily Living Questionnaire: a validation study in patients with dementia. Alzheimer Dis Assoc Disord. 2004 Oct-Dec;18(4):223-30. PMID: 15592135

Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, Lopez OL, DeKosky ST. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000 Spring;12(2):233-9. PubMed PMID: 11001602

Lee R.M., and Robbins S.B. 1995. Measuring Belongingness: The Social Connectedness and the Social Assurance Scales. Journal of Counseling Psychology. 1995. Vol. 42. No. 2. 232-241

Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 2015;**385**(9984):2255-63 doi: 10.1016/S0140-6736(15)60461-5.

Okereke OI, Rosner BA, Kim DH, et al. Dietary fat types and 4-year cognitive change in community-dwelling older women. Ann. Neurol. 2012;**72**(1):124-34 doi: 10.1002/ana.23593.

Papp KV, Rentz DM, Orlovsky I, Sperling RA, Mormino EC. Optimizing the preclinical Alzheimer's cognitive composite with semantic processing: The PACC5. Alzheimers Dement (NY) 2017;**3**(4):668-77 doi:10.1016/j.trci.2017.10.004.

Schinka JA, McBride A, Vanderploeg RD, Tennyson K, Borenstein AR, Mortimer JA. Florida Cognitive Activities Scale: initial development and validation. J Int Neuropsychol Soc. 2005;11(1):108-116.

Smith JC, Lancaster MA, Nielson KA, Woodard JL, Seidenberg M, Durgerian S, Sakaie K, Rao SM. Interactive effects of physical activity and APOE-ε4 on white matter tract diffusivity in healthy elders. Neuroimage. 2016 May 1;131:102-12. doi: 10.1016/j.neuroimage.2015.08.007. PubMed PMID: 26265157;

Sobol NA, Hoffmann K, Frederiksen KS, Vogel A, Vestergaard K, Brændgaard H, Gottrup H, Lolk A, Wermuth L, Jakobsen S, Laugesen L, Gergelyffy R, Høgh P, Bjerregaard E, Siersma V, Andersen BB, Johannsen P, Waldemar G, Hasselbalch SG, Beyer N. Effect of aerobic exercise on physical performance in patients with Alzheimer's disease. Alzheimers Dement. 2016 Dec;12(12):1207-1215. doi: 10.1016/j.jalz.2016.05.004. PubMed PMID: 27344641.

Vleet TV, DeGutis J, Dabit S, Chiu C. Randomized control trial of computer-based rehabilitation of spatial neglect syndrome: the RESPONSE trial protocol. BMC Neurol. 2014 Feb 7;14:25. doi: 10.1186/1471-2377-14-25. PubMed PMID: 24502769; PubMed Central PMCID: PMC3922254.

Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J. Clin. Epidemiol. 1993;**46**(2):153-62.

Wijndale K, De Bourdeaudhuij I, Godino JG, Lynch BM, Griffin SJ, Westgate K, Brage S. Reliability and validity of a domain-specific last 7-d sedentary time questionnaire. Med Sci Sports Exerc. 2014;46:1248–1260.

Wilson RS, Mendes De Leon CF, Barnes LL, et al. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. JAMA 2002;**287**(6):742-8.