The BrainHealth Project – Pilot Study
Study Protocol and Statistical Analysis Plan

NCT04621240
IRB# 20-32

Principal Investigator:
Sandra Chapman

November 25, 2019

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- Completion of Human Subjects Protection Training

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements.

Site Investigator:*

Signed: Sandra Chapman Date: 11/25/2019

Name
Title

** The protocol should be signed by the local investigator who is responsible for the study implementation at his/her specific site; ie, if Investigational New Drug study, the individual who signs the Form FDA 1572.*

List of Abbreviations

Statement of Compliance i
Signature Page ii
Protocol Summary ii

1 Key Roles 3
2 Background Information and Scientific Rationale 4
2.1 Background Information 4
2.2 Scientific Rationale 6
2.3 Potential Risks and Benefits 6
2.3.1 Potential Risks 6
2.3.2 Known Potential Benefits 6
3 Objectives 7
4 Study Design 8
5 Study Population 9
5.1 Selection of the Study Population 9
5.2 Inclusion/Exclusion Criteria 9
6 STUDY PROCEDURES/EVALUATIONS 10
6.1 Study Procedures 10
7 Statistical Considerations 12
7.1 Study Outcome Measures 12
7.2 Size Considerations 12
7.3 Participant Enrollment and Follow-Up 12
7.4 Analysis Plan 12
8 Subject Confidentiality 13
9 Informed Consent Process 14
10 Literature References 15

Title: The BrainHealth Project – Pilot Study

Population: Up to 200 cognitively healthy adults; aged 18-100; English speaking with internet access and a device

Number of Sites: 1

Study Duration: 9 months

Subject Duration: 3 months

Objectives:

Primary:

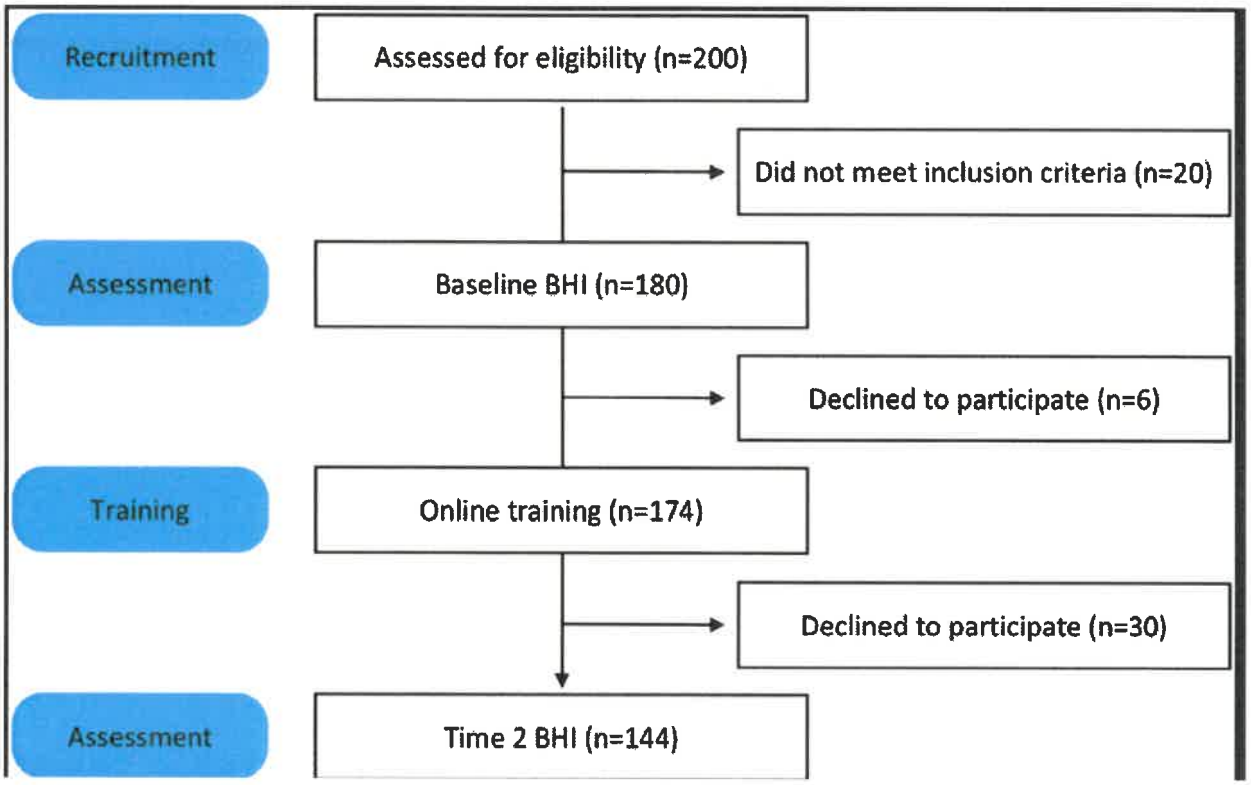
- Change in BrainHealth Index (BHI) pre-to-post training

Secondary:

- Develop an exploratory factor model of a BrainHealth Index derived from the assessments in the domains of cognition, well-being, real life, and social interaction

[NOTE: Brain imaging was initially planned as part of this pilot study but was not administered due to COVID-19 restrictions at the time.]

Participant Flow Diagram



1 KEY ROLES

For questions regarding this protocol, contact Erin Venza at erin.venza@utdallas.edu.

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Dr. Sandra Chapman, PhD, (PI), has been a PI on a numerous research projects examining the cognitive, emotional, functional, and neural impacts of cognitive interventions, specifically a strategy-based intervention that stems from gist-reasoning research known as SMART (Strategic Memory Advanced Reasoning Training). These studies examined multiple populations, all through in-person research, including healthy adults, individuals with traumatic brain injury (TBI) and mild cognitive impairment (MCI), to name a few.

Multiple trials funded by the National Institutes of Health (NIH), Department of Defense (DOD), and private philanthropy, have demonstrated that SMART can promote gains in core cognitive areas and strengthen several of the brain's key networks – functions that support planning, reasoning, decision-making, judgment, and emotional regulation. The program's effectiveness has been tested in multiple populations and remains distinct from other brain training programs, driven by an evidence base that is continuing to build, including studies in:

Population	Published Articles
Healthy Adults	Randomized: Chapman, Aslan et al., 2015; Chapman et al., 2016, 2017; Gallen et al., 2016; Motes et al., 2018
	Non-Randomized: Anand et al., 2010; Chapman et al., 2021; Laane et al., 2022
Adults with TBI or Stroke	Randomized: Han et al., 2017, 2018; Han, Martinez, et al., 2018; Samuelson et al., 2020, 2021; Vas et al., 2011, 2015
	Non-Randomized: Vas et al., 2017, 2020
Typical and disadvantaged adolescents	Randomized: Gamino et al., 2010
	Non-Randomized: Gamino et al., 2014, 2022; Motes et al., 2014
Children & teens with TBI	Randomized: Cook et al., 2014
	Non-Randomized: Cook et al., 2020
Adults with Mild Cognitive Impairment	Randomized: Das et al., 2019; Mudar et al., 2016
Adults with Bipolar Disorder	Non-Randomized: Venza et al., 2016
Adults with Rheumatoid Arthritis	Randomized: Blalock et al., 2020
Military Personnel & Law Enforcement	Non-Randomized: Young et al., 2021

Prior to 2020, our studies relied on in-person procedures with trained study personnel, significantly limited our reach. In order to make a shift to remote assessments, training, and interactions, we propose a pilot study of 200 healthy adults aimed at informing and perfecting the protocols for the larger study.

2.2 Scientific Rationale

Brain health depends on the complex, interwoven interactions of these multifaceted processes (cognition, well-being, social, life habits/responsibilities) and therefore should not be addressed independently of each other. For this reason, a composite brain health measure is needed. A supplemental aim of this study is to develop an exploratory factor model of a BrainHealth Index derived from the assessments in the domains of cognition, well-being, real life, and social interaction. Change in the BrainHealth Index is our primary outcome measure for the study.

Our study population for this pilot study will include individuals who self-report being cognitively healthy (no significant neurogenic or psychiatric impairment) and are older than 18 years of age. Given that the study is conducted in English and online, participants will be English speaking and will have access to internet and a device.

2.3 Potential Risks and Benefits

This study has minimal risks. Given that we were unable to conduct the imaging portion of this pilot study, risks are limited to potential fatigue, boredom or stress that participants may experience during the online assessments or trainings.

2.3.1 Potential Risks

Describe in detail any physical, psychological, social, legal, economic or any other risks to subjects that the PI foresees, as to each of the following:

- Boredom, fatigue or possible stress related to difficult cognitive tasks or questionnaires. Participants can take breaks to minimize those symptoms.
- Any time information is collected in research, there is a risk of loss of confidentiality. We will collect and protect data in agreement with institutional regulations to minimize this risk.

2.3.2 Known Potential Benefits

The research objectives of this study address issues that are ubiquitous in American society today including, higher stress, poor problem-solving skills (based upon the Organization for Economic Co-operation and Development data), age-related brain health decline, and anxiety. The research described herein enables collection of data on the efficacy of a proactive approach to holistic brain health. Collected data will be used to inform additional research to refine approaches to both assessing and improving brain health.

3 OBJECTIVES

- The first major goal of the present pilot study was to test an online system for: (1) remote delivery and collection of assessments; (2) remote delivery of a set of training modules; and (3) the feasibility of virtual coaching sessions with individual participants.
- The second major goal of this pilot study was to develop an exploratory factor model of a BrainHealth Index (BHI) derived from the assessments in the domains of cognition, well-being, real life, and social interaction, and to measure change in the BHI from pre-to-post intervention.

4 STUDY DESIGN

This pilot study is a single-arm intervention study. We plan to recruit up to 200 individuals within 6 months. Study participation will last 3 months. Participants will complete an online baseline assessment, then go on to engage with online cognitive training and coaching, and then will take their second assessment at Month 3.

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The second major goal of this pilot study was to develop an exploratory factor model of a BrainHealth Index (BHI) derived from the assessments in the domains of cognition, well-being, real life, and social interaction, and to measure change in the BHI from pre-to-post intervention.

5 Study Population

Our study population for this pilot study will be individuals who self-report being cognitively healthy (no significant neurological or psychiatric impairment that could interfere with participation) and are older than 18 years of age. Given that the study is conducted in English and online, participants will be English speaking and will have access to internet and a device.

5.1 Selection of the Study Population

We will recruit up to 200 participants from the general public. We expect to have more from the north Texas region (given our location); however, we are not limited by location since participation is online. We will advertise the study through our website and social media. Interested individuals can complete an online screener to see if they meet study inclusion/exclusion criteria. This study is open to all races and ethnicities.

5.2 Inclusion/Exclusion Criteria

Inclusion criteria will include: 18 years or older, able to access the internet (including access to a computer/smartphone/tablet), and being a proficient English speaker.

Potential participants were excluded for any of the following reasons: being under age 18, having a diagnosed neurological disorder, diagnosed psychotic disorder or uncontrolled psychiatric disorder, history of brain injury, or any uncontrolled health issues. It is important to note participants were not excluded for general health risk factors (ex: obesity, diabetes, and autoimmune conditions).

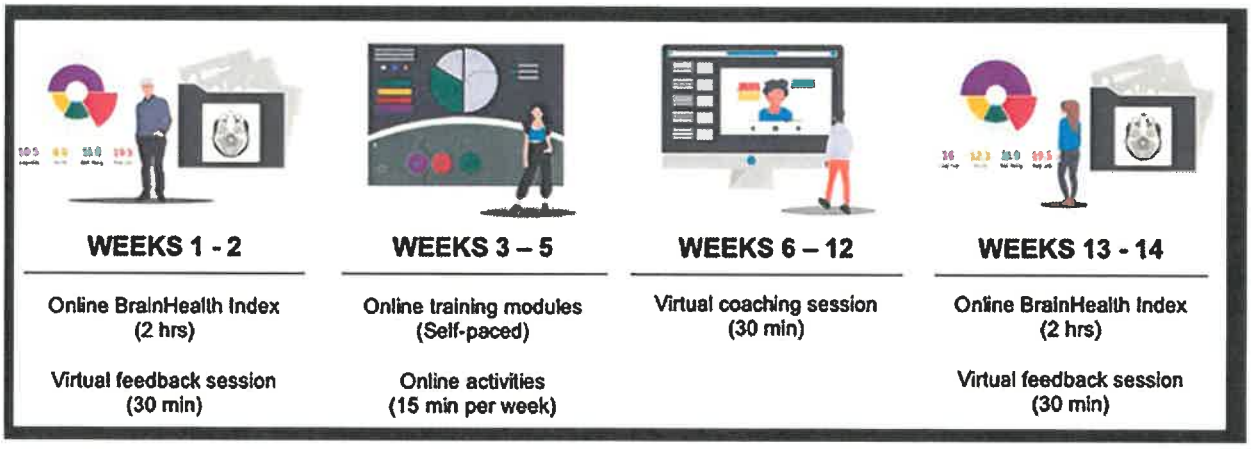
6 STUDY PROCEDURES/EVALUATIONS

6.1 Study Procedures

- This is a non-randomized, phase one pilot intervention trial designed to examine the behavioral benefits from an online training protocol.

- First, participants will complete their baseline BrainHealth Index assessment online. Following that, participants will have their first coaching call with a BrainHealth coach to discuss their BrainHealth Index results and get recommendations for interacting with the online training based on those results. BrainHealth Index results are stored in an online database. Training will consist of tactical brain strategies, derived from in-person SMART research (see image below), that are applicable to a multitude of circumstances, decisions, and goals. During weeks 3–5, participants will complete self-paced online training modules. Week 6 includes a halfway-point coaching call intended to motivate participants to continue implementing what they learned in training into real-life. Weeks 7–10, participants will continue working through training modules. Week 11, participants will take their 2nd BrainHealth Index. Week 12, participants will have their third coaching call.

Timeline of procedures



Overview of training modules

Module	Description	Time
1. SMART 1	Provides strategies and interactive acitvities on how to block irrelevant information and focus on key priorities (strategic attention). Example: Prioritize how you spend your time based on cognitive effort—each day identify top two tasks that requier the most deeper level thinking.	30 min
2. SMART 2	Includes strategies and interactive activities on how to abstract big-picture concepts from information to better inform real life decisions (integrated reasoning). Example: Extract key concepts from incoming information vs. trying to take in and remember everything.	30 min
3. SMART 3	Includes strategies and interactive activities on how to generate multiple and diverse perspectives/interpretations to strengthen mental flexibility (innovation). Example: Identify multiple alternative ideas/perspectives on divisive issues.	30 min
4. SMART 4	Consists of real-life application scenarios where participants can practice dynamic implementation of the strategies from SMART 1-3 (strategic attention, integrated reasoning, and innovation) in a cohesive manner. Example: Think about and prepare for a difficult conversation with someone you care about (considering their perspective, identifying the real issue at hand etc.).	30 min
5. Stress Solution 1	Presents the physiological and neurological response to stress, as well as cognitive strategies (linking with SMART) to manage and reframe stressors. Example: Reframe your perception of your response to a difficult situation from anxiety to excitement.	20 min
6. Stress Solution 2	Includes accessible techniques to help "recharge your battery" in times of stress or fatigue, as well as education on lifestyle factors that can positively impact our overall health. Example: Take several short breaks throughout your day.	20 min
7. Stress Solution 3	Provides research on the benefits of mindfulness, meditation, and healthy sleep habits, as well practical tips on how to practice each one (linking with SMART). Example: Participate in a meditation exercise.	20 min
8. Sleep	Presents research from Dr. Russell Foster on the science behind sleep, the brain impact of poor sleep, and practical tips for improving one's sleep habits.	20 min
9. COVID-19 Information	Safety tips from an emergency medicine physician on how to protect ourselves and others during the COVID-19 pandemic.	5 min

Modules 1-7 consisted of videos teaching tactical brain strategies and application exercises. Modules 8-9 were informational videos only.

7 STATISTICAL CONSIDERATIONS

7.1 Study Outcome Measures

Brain health depends on the complex, interwoven interactions of these multifaceted processes (cognition, well-being, social, life habits/responsibilities) and therefore should not be addressed independently of each other. For this reason, a composite brain health measure is needed. A supplemental aim of this study will be to develop an exploratory factor model of a BrainHealth Index derived from the assessments in the domains of cognition, well-being, real life, and social interaction. Change in the BrainHealth Index was our primary outcome measure for the study.

Data collected from this pilot study will be used to develop a modified BrainHealth Index, one that does not rely on fixed wights by consensus but, rather, one that allows estimated weights for variables on a natural scale. This will be accomplished by fitting an exploratory factor model of the inter- and intra-domain correlations of online assessments.

7.2 Size Considerations

We will pilot n=180 participants, expecting around n=150 to complete time 2 assessments. This will be a sufficient sample size to conduct an exploratory factor analysis of change in the online assessments.

7.3 Participant Enrollment and Follow-Up

We enrolled 180 participants at baseline and 144 completed the study.

7.4 Analysis Plan

Statistical analysis plan:

General linear models will include 1) assess mean changes in the BHI; 2) assess the influence of age and gender on BHI change; 3) asses the effect of training completion rates on BHI change. Development of a data-driven brain health index will be accomplished by fitting an exploratory factor model of the inter- and intra-domain correlations of 3-month change in assessments. Weights obtained from the latent factor model will be used to transform individual assessments to brain health factor indices.

8 SUBJECT CONFIDENTIALITY

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Personally identifiable information (PII) will be removed at study closure; de-identified data collected within the online dashboard will remain there. Additionally, participants in this pilot will have the option to consent into the larger BrainHealth Project study and carry forward their pilot data at the end of pilot study.

9 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. As consenting for this study will be delivered remotely online, participants can take their time reviewing the form, in the comfort of their own space, and considering before signing. Subjects will have the opportunity to discuss any questions around the consent form with study personnel, by request. The subjects may withdraw consent at any time throughout the course of the study. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10 LITERATURE REFERENCES

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