Title: A Pilot of Methylphenidate in Mild Cognitive Impairment and Dementia Participants.

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A Pilot Multiple Crossover, Randomized Block Sequence, Double-Blind, Placebo-Controlled Trial for Use of Methylphenidate for Cognitive and Behavioral Symptoms in Mild Cognitive Impairment and Dementia

Steven E. Arnold MD
Principal Investigator
Massachusetts General Hospital

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institutional review boards or to duly authorized representatives of the US Food and Drug Administration or national regulatory authority under the condition that they maintain confidentiality.

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP), and the applicable regulatory requirements, United States Code of Federal Regulations (CFR) Title 45 CFR Part 46 and Title 21 CFR Parts 50, 56, and 312.

SIGNATURE PAGE

I have read the attached protocol, A Pilot Multiple Crossover, Randomized Block Sequence, Double-Blind, Placebo-Controlled Trial for Use of Methylphenidate for Cognitive and Behavioral Symptoms in Mild Cognitive Impairment and Dementia and agree to abide by all described protocol procedures. I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 54, and 312, local Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

Investigator:_____

Signed: _____ Date: _____

LIST OF ABBREVIATIONS

ABID	Agitated Behavior in Dementia Scale
AD	Alzheimer's Disease
ADC	Alzheimer's Disease Center
ADCS-ADL-MCI	Alzheimer's Disease Cooperative Studies-Activities of Daily Living-for Mild Cognitive Impairment
ADRD	Alzheimer's Disease and Related Dementias
AES	Apathy Evaluation Scale
BAI	Beck Anxiety Inventory
BVMT-R	Brief Visual Memory Task-Revised
CFR	Code of Federal Regulations
C-SSRS	Columbia Suicide Severity Rating Scale
CPT	Continuous Performance Test
CRF	Case Report Form
CSF	Cerebrospinal Fluid
eCRF	Electronic Case Report Form
ECG	Electrocardiograph
EDC	Electronic Data Capture
EEG	Electroencephalogram
FAQ	Functional Activities Questionnaire
FDA	Food and Drug Administration
GDS	Geriatric Depression Scale
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Internal Review Board
MADRC	Massachusetts Alzheimer's Disease Research Center
MCRCT	Multicrossover Randomized Controlled Trial
MCI	Mild Cognitive Impairment

MDU	Memory Disorders Unit
MoCA	Montreal Cognitive Assessment
MPH	Methylphenidate
NACC	National Alzheimer's Coordinating Center
NIA	National Institute on Aging
PBO	Placebo
PCP	Primary Care Physician
PI	Principal Instigator
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UDS	Uniform Data Sat
US	United States

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1 ETHICS/PROTECTION OF HUMAN SUBJECTS

1.1 Institutional Review Board (IRB)

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs.

1.2 Ethical Conduct of Study

The study will be conducted in accordance with GCP defined by the International Conference on Harmonisation (ICH) and the ethical principles of the Declaration of Helsinki.

1.3 Subject Information and Consent

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations, and ICH Guidance Documents pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, subjects will be informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits. Subjects will be given adequate time to ask questions and become familiar with the study prior to providing consent to participate. Subjects will give their written consent to participate in the study and will be provided with a copy of the fully executed consent form for their records.

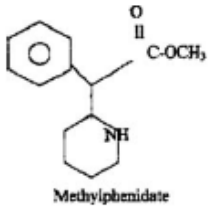
2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Alzheimer's Disease (AD) Overview

Alzheimer's disease (AD) is the most prevalent form of dementia affecting more than 5,000,000 subjects in the US and an estimated 20,000,000 people worldwide, according to the Alzheimer's Association (1). AD causes progressive neuronal degeneration, resulting in progressive memory loss and dementia. AD has no available cure; however, treatments exist that can very modestly ameliorate dementia symptoms. There are currently only four FDA-approved medications for the symptomatic treatment of AD, but many new therapeutic approaches are being investigated. Some of these approaches involve new pharmaceutical agents while others use existing FDA-approved drugs in novel ways to combat AD symptoms. One such drug, methylphenidate (MPH), which is typically used to treat ADHD, has come of interest to determine its efficacy in relieving some of the behavioral and cognitive symptomology commonly seen in AD (2).

2.2 Methylphenidate (MPH)

Chemical Structure of MPH (2)**:**



Methylphenidate

Methylphenidate (MPH) is a phenethylamine/benzylpiperidine psychostimulant drug, first approved by the FDA in 1955 for treatment of "hyperactivity," now known as attention deficit hyperactivity disorder (3) and it is now the most common treatment of the disorder (4). MPH not only alleviates symptoms of ADHD, but also seems to have beneficial effects in other disorders and populations. Treatment with MPH at therapeutic doses has been shown to improve performance on working memory tasks in rodents, normal subjects, and ADHD subjects (2,5,6).

The therapeutic use of MPH has expanded to ameliorate cognitive dysfunction due to various medical and neurological disorders, fatigue, depression, and more (2). Research studies and clinical experience have generally found MPH to be safe for use in a variety of populations, from children to the elderly and healthy controls to patient populations. It has been approved for symptomatic treatment of narcolepsy, and common off-label uses include depression especially in terminal illness and palliative care (2,7), geriatric depression (8) and for augmentation of antidepressant medication (9) and fatigue (especially cancer-related)(2). Usefulness of MPH has also been suggested for neuroprotection against Parkinson's disease(5), general memory and attentional cognitive enhancement (10,11), and apathy in Alzheimer's disease(12–15).

MPH is commonly prescribed in various neurodegenerative dementias, but cognitive and behavioral efficacy data from rigorous clinical trials are scant. Safety and tolerability in elderly patients with dementia is generally well-established. Improvements in apathy have been reported in clinical trials in Alzheimer's disease (12–16) and to

lesser degrees, in vascular dementia (17), Parkinson's disease (18), geriatric depression (8) and stroke (14). While not the primary outcome of these studies, occasional improvements have also been noted in attention (19), inhibition (20), and negative symptoms (17).

Of particular relevance to the present study is an "N of 1" trial of methylphenidate in five elderly patients (16), three of whom were experiencing depression and two of whom were suffering from chronic apathy due to mild-moderate dementia. The trial started with a two-week baseline period followed by five one-week treatment blocks in which patients took either MPH (5 mg twice daily) or placebo for two days. At the conclusion of the five weeks, two of the three depressed patients and one of the two apathetic patients showed significant improvements on clinical measures of depression and apathy respectively. The remaining apathetic patient was discontinued because they were unable to complete the Apathy Evaluation Scale. This trial shows that MPH could be an effective treatment for depression and apathy, both of which are common behavioral symptoms of AD, and demonstrates the feasibility of a 'N of 1" multi-crossover design in similar elderly, cognitively impaired populations that we will study here.

2.2.1 **Mechanism of Action**

MPH works to inhibit catecholamine reuptake primarily by blocking pre-synaptic dopamine and norepinephrine transporters and thus increasing concentrations of dopamine and norepinephrine (21) 3- to 4- fold in the synaptic cleft as measured in striatum and prefrontal cortex (6,22). The striatum is involved in reward and reinforcement while the prefrontal cortex is involved in directing goal-driven behaviors and response inhibition, all of which are cognitive areas commonly affected by AD (23). It is plausible that the catecholamine reuptake inhibition in these areas is responsible for the cognitive, behavioral, and emotional changes that result from treatment with MPH (21). It is also a weak agonist of the 5HT1A receptor, which is involved in dopaminergic regulation and therefore depression, learning, and memory (24–26).

MPH is available in multiple forms, including immediate-release oral formulations as well as extended and sustained release oral forms and transdermal patches. The present trial will use CONCERTA® or an equivalent generic, extended release form of MPH.

2.2.2 **Pharmacokinetics**

Concerta® or equivalent generic (22) extended-release MPH tablets are formulated for once-daily administration and follow a biphasic pharmacokinetic profile to provide day-long medication availability. Following oral administration of Concerta®, plasma concentrations of MPH increase rapidly reaching an initial maximum at about 1 hour, followed by a gradual further increase in concentration over the next 5 to 9 hours. Thereafter, concentrations gradually decrease. Tmax across all doses occurs between 6 to 10 hours. The half-life of methylphenidate in adults and adolescents after oral administration of Concerta® is about 3.5 hours. The Concerta® or generic extended release MPH used in this study minimizes the alternation between peak and trough plasma concentrations that occur with use of standard MPH (see Figure 1 below). Metabolism of MPH is extensive predominately via de-esterification by carboxylesterase CES1A1 to alpha-phenyl-piperidine acetic acid (ritalinic acid) which has little to no pharmacologic activity (2).

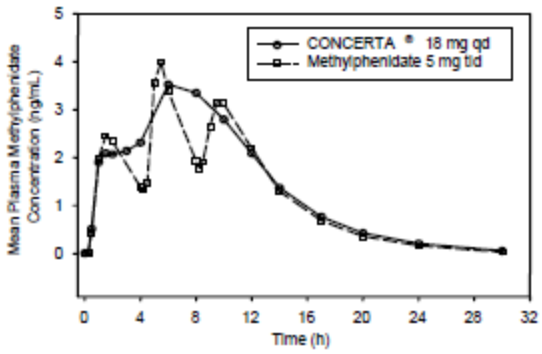


Figure 1. Mean MPH plasma concentration after one dose of Concerta® 18 mg q.d. and immediate-release MPH 5 mg every 4 hours(22)

3 SPECIFIC AIMS

3.1 Overall Study Design and Plan

The study uses a double-blinded, multi-crossover, randomized controlled trial design (27). Multi-crossover, randomized controlled trial designs in AD allow for each subject to serve as their own control as they progress through several randomized blocks of experimental treatment and placebo. As such, multi-crossover studies carried out with systemically applied outcome measures, pre-specified doses of study drug, and necessary treatment and washout periods serve as unbiased estimates of treatment effect for individual subjects. When data from several subjects are analyzed together following such a N-of-1 design, substantial increases in statistical power is afforded with a fraction of the subjects and assessments required for similar levels of power in conventional parallel group trials. For example, based on data from a recent single crossover pilot study on the effects of metformin on patients with MCI and early dementia (28), we estimated that in a multi-crossover trial, less than 10% of the subjects of a conventional parallel group study would be required to achieve equivalent 80% power (29). The relative stability and slow progression of cognitive and functional AD symptoms (28,30–33) is well-suited to detect symptomatic benefit within the multiple, reasonably short blocks of outcome measuring associated with multi-crossover design.

Given its pharmacokinetic and pharmacodynamic profile, especially its rapid onset and rapid cessation of action with little carry over effect, MPH is a suitable drug for a multi-crossover, randomized controlled trial in which relatively brief active drug or placebo treatment periods are alternated and effects can be determined at an individual participant level. Relevant cognitive functions and behaviors can be sensitively monitored in each condition with standard and novel ecological measures.

This study will be conducted entirely virtually other than an optional in-person screening visit. Subjects will not be required to come in to MGH for any research visits. Visits will be conducted over the phone or over a HIPPA-compliant, encrypted videoconferencing platform such as Partners Zoom for Healthcare. This trial will help to determine whether or not a trial can be conducted entirely virtually in an ADRD population.

This is a single-site, multiple crossover, double-blind placebo (PBO)-controlled randomized sequence block trial of MPH vs. PBO I n approximately eight volunteers with mild cognitive impairment (MCI) or mild-stage Alzheimer's Disease and Related Disorders (ADRD). Over the 16-week study, each volunteer will move through

four, 4-week treatment periods: a PBO lead-in, acclimation period followed by three, crossover MPH vs PBO "blocks" (See Figure 2 below). Each “block” will consist of treatment with MPH for two-weeks and treatment with PBO for two-weeks; each block order will be randomly assigned. Thus, all volunteers will receive a total of 10 weeks of PBO and 6 weeks of MPH. Subjects will have standardized cognitive, mood, and functional assessments at the baseline experimental visit as well as at each crossover. Daily cognitive function will be assessed by performance in computer games involving memory, attention, and executive functioning. Daily activity and sleep will be assessed with a wrist actigraph. Our target enrollment for this pilot study is eight subjects.

Subjects will be randomized into one of six counter-balanced block sequences (see Figure 2 below). Randomization will be done by a non-clinical study staff statistician. All on-site study staff will be blinded to the subjects’ block treatment assignment. Randomization will be such that there is at least 1 subject per sequence.

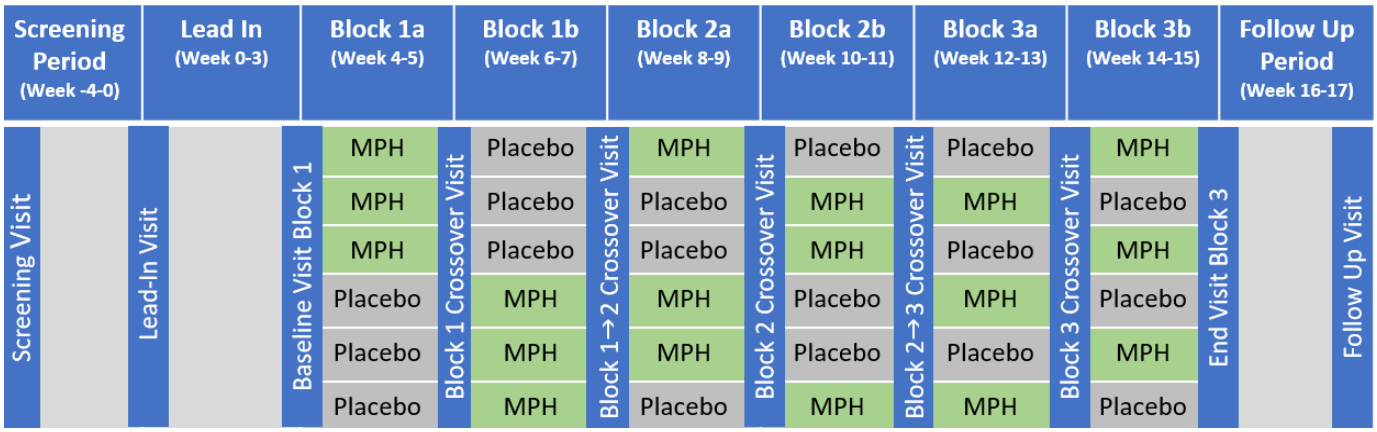


Figure 2 Trail Design Schema- Each subject will be randomized into one of six block randomization sequences such that each sequence will have at least one subject assigned to it.

3.2 Study Objectives

The primary objective of this clinical trial is:

1. to pilot the feasibility of a virtual MCRCT design in approximately 8 participants with MCI or mild-stage dementia due to AD/ADRD.

The secondary objective will be:

2. To examine the efficacy of MPH on cognition as measured by daily cognitive assessments compared to more standard single time-point neuropsychological outcome measures.

The exploratory objectives are:

3. To investigate the effects of MPH compared to placebo on neuropsychiatric and daily functioning with standard measures, home-based actigraphy, and other novel digital cognitive and neurophysiological assessment.

Analyses will primarily focus on within-participant comparisons. Due to the small sample size of this pilot, between-participant comparisons will be exploratory and findings will be used to inform the design of larger MCRCTs.

3.3 Protocol Adherence

Each Investigator must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by Internal Review Board (IRB). Each investigator will be responsible for enrolling only those study subjects who have met protocol eligibility criteria.

4 SUBJECT SELECTION

4.1 Inclusion/exclusion Criteria

Investigators will use their best clinical judgment when selecting potential research subjects for this study and will not enroll any individuals who are frail or in questionable health, even if they meet all inclusion/exclusion criteria.

4.1.1 Inclusion Criteria

Study subjects meeting all of the following criteria will be allowed to enroll in the study:

1. Aged 55-95 inclusive;
2. Diagnosis of MCI or mild-stage dementia presumed due to AD and AD-related disorders;
3. Cognitive abilities sufficient to be able to complete all study tasks as determined by the PI or a Co-I;
4. Education level, English language skills, and literacy that indicates participant will be able to comprehend all assessments;
5. Neuropsychiatric Inventory Agitation/Aggression Question 4 = "No" or "Yes" with a mild severity rating.
6. Willing and able to complete all assessments and study procedures;
7. Not pregnant, lactating, or of child-bearing potential
8. Volunteer has a Study Partner with at least two days per week of contact and willing to complete partner study forms;
9. No exclusionary medications or dietary supplements. See Section 6.5.8.1
10. If on cholinesterase inhibitor and/or memantine, doses are stable for 3 months prior to baseline.
11. Basic video conferencing capabilities and a willingness to participate in a virtual trial (including self-administration of ECG).

4.1.2 Exclusion Criteria

Subjects meeting any of the following criteria during the screening evaluation will be excluded:

1. Any history of specific CNS disease other than AD or AD-related disorders, such as major clinical stroke, brain tumor, normal pressure hydrocephalus, multiple sclerosis, significant head trauma with persistent neurological or cognitive deficits or complaints;
2. Clinically significant or unstable medical condition that could affect safety or compliance with the study and would, in the opinion of the investigator, pose a risk to the participant if they were to participate in the study;
3. Major active or chronic psychiatric illness (e.g. depression, bipolar disorder, obsessive compulsive disorder, schizophrenia) within the previous year;
4. Current suicidal ideation or history of suicide attempt;
5. History of alcohol or other substance abuse or dependence with the past two years;
6. Clinically significant abnormalities on complete blood count, comprehensive metabolic panel, B12, or TSH screening safety lab results;

7. Concomitant use of medications with psychoactive properties that may deleteriously affect cognition (anticholinergics, antihistamines, antipsychotics, sedative hypnotics, anxiolytics);
8. Treatment with monoamine oxidase inhibitors, coumadin, phenobarbital, phenytoin, primidone, tricyclic antidepressants or other medicines with potential for clinically significant interaction;
9. Hypersensitivity to MPH;
10. History of marked anxiety and agitation, ADHD, motor tics, glaucoma, or a history or family history of Tourette's Syndrome;
11. Clinically significant cardiac condition for which MPH may be contradicted as determined by study physician, such as MI or ventricular arrhythmia within 6 months of enrollment;
12. History of untreated, uncontrolled hypertension or a blood pressure greater than 150/90 during the screening period;
13. Use of other small molecule or device- based investigational agents one month prior to entry and for the duration of the trial.

4.1.2.1 Women of Childbearing Potential (WOCBP)

For the purposes of this study, women of childbearing potential are defined as all women who are capable of becoming pregnant, unless they meet one of the following criteria:

1. 12-months post-menopausal
2. Post-hysterectomy
3. Surgically sterile

If a female subject does not meet these criteria and is considered of childbearing potential they will be excluded from the clinical trial.

4.2 Recruitment

Approximately twelve subjects will be screened, and after screening we expect eight subjects to complete the study. Some subjects may be recruited from the longitudinal cohort being followed at the Massachusetts Alzheimer Disease Research Center (MADRC) at MGH. These subjects have agreed to be contacted for research purposes and will be given the opportunity to participate in this project.

4.2.1 Recruitment of Subjects through Advertising

Advertisement flyers will be posted on bulletin boards around MGH (both the main campus and Charlestown campus) to advertise for the study as well as an advertisement on Partners Rally for Research. A phone number will be provided that will ring directly to the research coordinator, and voice messages can be left for the coordinator on a password-protected voice mailbox. A recruitment brochure will also be used in conjunction with other recruitment strategies to distribute to potentially interested research participants and their families in order to provide them with a tangible resource explaining the details of the trial.

4.2.2 Recruitment of Subjects Identified through Private Medical Information

MGH Memory Disorders Unit physicians will be made aware of the study, including eligibility criteria. If they feel that a patient of theirs may be a candidate for the study, they will either 1) present the patient with a recruitment letter, 2) obtain the patient's permission to be contacted by the study staff and give the study coordinator the patient's contact information, or 3) inform the patient of the study coordinator, who will be present in a private waiting area of the Wang Ambulatory Care Center's Neurology clinic. If the patient approaches the study coordinator, the study coordinator will discuss recruitment with the subject and their family member at the end of a scheduled clinic

visit. The research coordinator will ask the patient if they would like to be contacted to hear about potential clinical trials. The coordinator will collect the patient's contact information and add it to a shared Memory Disorders Unit (MDU) database. After the patient has been deemed potentially eligible to participate in this study by a doctor. A study coordinator will contact the subject and explain study in further detail and if the subject is interested, potentially complete a telephone prescreening.

4.2.2.1 Recruitment of Subjects from the Massachusetts Alzheimer's Disease Research Center

Subjects will also be recruited from an observational study that follows a longitudinal research cohort (LC) of approximately 500 active research participants recruited from the MGH's own Memory Disorders Unit clinic and other diverse sources. LC subjects are followed-up on an approximately annual basis, either in-person at the MGH or by means of a telephone follow-up 'visit'. As of Dec 1, 2016, approximately 25% of the cohort are cognitively-normal subjects, approximately 37% have a dementia diagnosis, and approximately 38% are diagnosed either with Mild Cognitive Impairment (MCI) or an 'impaired, not MCI' diagnosis.

A Uniform Data Set (UDS) mandated by the National Institute on Aging (NIA) for all federally-funded Alzheimer's Disease Centers (ADCs) is collected from each participant at annual research visits, and these data are then submitted to the National Alzheimer's Coordinating Center (NACC). Additional neuropsychological tests, biomarker data and imaging data that are not part of the UDS are also collected locally by the Massachusetts Alzheimer's Disease Research Center (MADRC) on these participants. The Partners IRB protocol that covers the "LC'' is protocol # 1999P003693 ('Alzheimer's Disease Research Center'; PI: Hyman)

Study staff will only contact subjects that have indicated to the MADRC that they are interested in hearing about / participating in other studies.

4.2.3 Recruitment of Subjects from among the Investigator's Own Patients

Dr. Steven Arnold is a neurologist in the MGH Memory Disorders Unit and subjects may also be recruited from among his patients. Special care will be taken to ensure patients are aware that their participation is completely voluntary and that their decision to participate will not affect their care. As with other clinicians in the Memory Disorders Unit, if the investigator has identified a patient as a potential candidate for the study, the investigator will either 1) present the patient with a recruitment letter, or 2) inform the patient of the presence of the study coordinator, who will be present in a private waiting area of the Wang Ambulatory Neurology clinic. If the patient approaches the study coordinator, the study coordinator will follow the procedure described in Section 4.2.2.

5 SUBJECT ENROLLMENT

5.1 Informed Consent Process

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations, and ICH Guidance Documents pertaining to informed consent.
Potential subjects will be given general information about the research (e.g., through informational sheets, letters, or discussion with their treating physicians). If they are interested in learning more about the study, they will then contact the research coordinator. The research coordinator will obtain verbal consent in accordance with Partner's

Prescreening Guidelines prior to performing a telephone prescreening interview. If the subject meets pre-screening criteria and wishes to continue the screening process, a screening visit will be scheduled.

The subject will have the option to do an in-person screening visit or a virtual screening visit if they are not comfortable coming in for or able to come in for an in-person screening visit due to the COVID-19 pandemic or physical distance from the study site.

At the screening visit, the study physician investigator or licensed nurse practitioner will meet with the potential subject either in-person or in a videoconference to review and discuss the details of the study using the informed consent document as a guide. A copy of the informed consent document will be sent to the subject and the study partner before the screening visit takes place, and they will have at least 24 hours between when the document is received and when the screening visit is scheduled in order for the subject and study partner to have adequate time to fully review the Informed Consent Document.

The informed consent discussion will include all of the required elements of informed consent, including the purpose of the research, the procedures to be followed, the risks and discomforts, as well as potential benefits associated with participation, and alternative procedures to study participation. Their questions will be answered to their satisfaction. The subject will be provided with adequate time to reflect on the potential benefits and risks and possible discomforts of participation, and to make an informed decision.

The informed consent process will be conducted using a REDCap-based electronic consent form. The consent form has been developed in REDCap, a secure, web-based, HIPAA-compliant, data collection platform with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data for other users. During the screening visit, the participant and study partner will be emailed a link to the REDCap e-consent form and the document will be reviewed with the participant and study partner by a licensed clinician investigator. The potential subject may ask to speak with the physician investigator should a licensed nurse practitioner be involved in obtaining informed consent.

Participant and study partner signatures will be obtained using electronic signature via mouse followed by electronic signature by the licensed clinician investigator. Upon completion of the informed consent process, participants will be provided with an electronic copy of the signed consent from, and an electronic copy will be stored in the REDCap database. If a participant and/or study partner prefers a hard copy of the consent form, it will be mailed to them.

If the virtual consent process via REDCap-based electronic consent form is unsuccessful, a second attempt at virtual consent will occur. This virtual consent process will include all aspects of an in-person consent and will follow the recommendations set forth by the Partners Human Research Committee on remote Consent. The subject and study partner will sign a hard copy of the Informed Consent document and mail it back to the study team. The investigator will sign the returned hard copy immediately upon receipt, and the hard copy will be stored in the subject's study binder.

If a subject is not deemed capable of providing consent by the physician investigator or licensed nurse practitioner, they will not be eligible to participate in the trial.

Since subjects may be enrolled from among the investigators' own clinical patients, steps will be taken to avoid any possibility for coercion. As detailed above, the investigators will not directly approach their patients regarding possible participation in the study. If an investigator has identified a patient as a potential candidate for the study, the investigator will notify the study coordinator before the patient is seen in clinic. The study coordinator will then approach the subject, independently, after the clinic visit is completed, to inquire if the patient may be interested in participating in the study. If the patient indicates that they are interested, they will be handed an information flyer, and will be asked to call the study coordinator at a time that is convenient for them. Other MDU physicians (not participating directly in the study) may also discuss the study directly with their patients, if they choose to do so. In each of these scenarios, the prospective participant will be given an informational flyer, and will be instructed to call the study coordinator at their convenience. In addition, subjects who are not scheduled to follow-up in clinic during the recruitment period may be mailed a letter from their physician, copies of which have been included with the IRB resubmission.

5.2 Remuneration

Subjects will be given $25 for the Screening Visit and for their participation in each subsequent visit involving cognitive and neuropsychiatric testing and blood draws for a total of up to $250 for 10 visits. After \ the final Follow-up visit, they will also receive a $100 bonus for completion of the study so long as they were at least 75% compliant with all study activities, including medication dosing, cognitive exercises, and wrist actigraphy tracking. Subjects have the potential to receive $350 total.

If subjects come in for an in-person screening visit, a meals and parking voucher will be offered at each visit. If appropriate, travel expenses will be reimbursed including mileage at 58 cents per mile up to $150.

5.3 Reasons for Withdrawal

A study subject will be discontinued from participation in the study if:

1. Any clinical adverse event (AE), concurrent illness, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.
2. The subject meets any exclusion criteria (either newly developed or not previously recognized) that the study physician deems to be a risk to continued participation.
3. Subjects are free to withdraw from participation in the study at any time upon request.

5.3.1 Handling of Withdrawals

A subject may choose to discontinue participation in the study at any time. An Early Termination visit will occur when a subject withdraws consent, i.e. withdrawing his or her participation in future study procedures.

5.4 Termination of Study

This study may be prematurely terminated if, in the opinion of the investigator, there is sufficient reasonable cause.

Circumstances that may warrant termination include, but are not limited to:

1. Determination of unexpected, significant, or unacceptable risk to subjects;
2. Unsatisfactory enrollment;
3. Insufficient adherence to protocol requirements;
4. Data that are not sufficiently complete and/or evaluable;

If the study is prematurely terminated or suspended, the investigators will promptly inform the institution and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the investigator, as specified by applicable regulatory requirement(s).

6 STUDY PROCEDURES

6.1 Study Visits

Table 1. Study Visit **Schedule**

Activity	Screening Visit	Week 0	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16	Early DC	Week 18
	Week (-4-0)	Lead-in Baseline	Block 1 Baseline	Block 1 Crossover	Block 1 End/Block 2 Baseline	Block 2 Crossover	Block 2 End/Block 3 Baseline	Block 3 Crossover	Block 3 End		Follow Up
Informed Consent[1]	X										
Demographics	X										
Medical History/Updated Medical History	X	X	X	X	X	X	X	X	X	X	X
Height and Weight[2]	X										
Vital Signs[3]	X	X	X	X	X	X	X	X	X	X	X
Inclusion/ Exclusion Review	X	X									
Safety Labs[4]	X										
ECG[4]	X	X	X	X	X					X	X
Physical and Neurological Examination or PCP Approval	X										
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric Assessment	X	X	X	X	X	X	X	X	X	X	
Neurocognitive Assessment	X	X	X	X	X	X	X	X	X	X	
Functional Assessment		X	X	X	X	X	X	X	X	X	
Technology Training/Check-in		X	X	X	X	X	X	X	X		

Randomization		X									
Dispense Drug		X	X	X	X	X	X	X			
Daily Lumosity Exercises		→	→	→	→	→	→	→	→		
Daily Mood and Sleep Ratings		→	→	→	→	→	→	→	→		
Daily Wrist Actigraphy		→	→	→	→	→	→	→	→		
AE Reporting[5]	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications and Supplements	X	X	X	X	X	X	X	X	X	X	X
Drug Accountability and Compliance			X	X	X	X	X	X	X	X	

[1] All subjects will be pre-screened over the phone by study staff to determine eligibility and to ensure that the subject is safe to undergo study procedures. Pre-screening procedures include: assess inclusion and exclusion criteria and review and document concomitant medications and therapies. During this call, study procedures will be discussed in detail and the subject will be given the opportunity to ask questions about the study. The written informed consent will be signed by the subject and the Study Investigator at the screening visit. All other study procedures will take place after signing an IRB-approved consent form.

[2] Height and weight will be self-reported.

[3] Vital signs include systolic and diastolic pressure in mmHg and heart rate/minute.

[4] Screening and safety bloodwork includes complete blood count, complete metabolic panel, serum B12 and folate testing, and serum thyroid Stimulating Hormone testing. Labs will be drawn at an off-site, certified, blood draw facility if the screening visit is conducted virtually.

[5] 6-Lead ECG will be performed for all subjects from the Screening Visit until Week 8 and at the Follow Up Visits. If there are no clinically significant abnormalities or changes in the ECGs during this time, ECGs will not be done at the remainder of the Crossover Visits. If new cardiac compliant occurs, ECGs will be resumed.

Table 2. Telephone Check- In Schedule

	Week 0	Week 1	Week 3	Week 5	Week 7
Technology Check-In	**X**	**X**	**X**		
Drug Compliance	**X**	**X**	**X**		
AE Reporting	**X**	**X**	**X**	**X**	**X**
Dosage Escalation[1]				**X**	**X**

[1] The dosage escalation phone call will consist of 2 parts- a before- and after- escalation phone call (See section 6.1.3.1).

6.1.1 **Screening Visit (Week -4)**

The following procedures will be performed to determine the subject's eligibility for the study and will take approximately 3 hours. If the subject elects to have a virtual screening visit, the visit will be broken up into 2 parts that will be completed within the 4-week screening window. The second portion will be completed after the subject has been shipped an at-home blood pressure monitor, oral thermometer, and the KardiaMobile 6L device.

- Obtain written informed consent from the subject
- Obtain demographics and medical history
- Administer neurocognitive assessment- MoCA
- Administer neuropsychiatric surveys- C-SSRS, GDS, and NPIQ
- Assess and document adverse events (AEs) after subject signs informed consent form (ICF)
- Review and document concomitant medications, supplements, and therapies
- Assess inclusion and exclusion criteria to determine subject eligibility
- At in-person screening visit
    - Measure vital sign, height and weight
    - Perform physical and neurological examination
    - Perform 12-lead electrocardiogram (ECG) if in person
    - Phlebotomy for safety labs in-person

OR

- For screening visit part 2:
    - Measure vital signs, self-report height and weight
    - Obtain letter from subject's primary care provider clearing them for participation in the trial in lieu of a physical/neurological exam
    - 6-Lead ECG with KardiaMobile device
    - Safety blood labs drawn at an off-site, certified, blood draw facility.

6.1.1.1 Screen Failures

Any subject who signs consent will be considered enrolled in the study. If a subject fails screening, *at a minimum,* the following information should be captured and entered into the Electronic Data System (EDC).

- Inclusion/Exclusion Criteria
- Demographics
- Reason for screen failures

6.1.2 **Lead-In Baseline- Week 0**

This visit will take place within 4 weeks of the Screening Visit as soon as the patient has been deemed eligible via Inclusion/Exclusion criteria. Prior to this visit, the subject will be shipped the Fitbit device and if requested, the laptop computer. The following procedures will be performed and will take approximately 2-3 hours.

- Measure Vital
- Assess inclusion and exclusion criteria to determine subject eligibility
- Randomization
- Administer neuropsychiatric and functional surveys, including C-SSRS, GDS, ABID, BAI, AES, FAQ, and ADCS-MCI-ADL (24)
- Administer neurocognitive assessments, including RBANS, CPT, BVMT-R, Trails, and speech production task
- Perform ECG
- Explain and practice how to use technological devices and software that will be used during study- laptop computer, daily brain game exercises, and Fitbit device
- Review and document concomitant medications, supplements, and therapies
- Dispense placebo
- Assess and document AEs

6.1.2.1 Technology Check-In Phone Calls- Weeks 0, 1, and 3

At Weeks 0**,** 1, and 3 during the initial Lead-in Period, a study coordinator will call the subject to ensure they understand how to use all technology and discuss compliance if necessary. The subjects will also be provided with the study coordinator's phone number and email and encouraged to contact the study coordinator with questions or concerns at any time.

6.1.3 **Block 1 Start, Crossover, and Block 3 End Visits- Weeks 4, 6, 8, 10, 12, 14, and 16**

This visit will take place 14 days ± 1 day after the previous visit. The following procedures will be performed and will take approximately 2 hours.

- Measure Vital Signs
- Technology Check-In
- Perform ECG
- Administer neuropsychiatric and functional surveys, including C-SSRS, GDS, ABID, BAI, AES, FAQ, and ADCS-MCI-ADL (24)
- Administer neurocognitive assessments, including RBANS, CPT-AX, BVMT-R, Trails, and speech production task
- Assess and document adverse events (AEs)
- Review and document concomitant medications, supplements, and therapies
- Dispense study drug/placebo – except at visit 16
- Assess drug accountability/compliance
- Assess and review technology use and compliance

6.1.3.1 Dose Escalation Telephone Check-In

After the lead-in period is completed, the subjects will begin the block period. At weeks 5 and 7, the subjects will be called by a licensed study clinician and if the subject seems to be tolerating the 1 capsule dose, the subject will be instructed to increase their dose from 1 capsule per day to 2 capsules per day (see section 6.5.4). To determine

safety and tolerability of the dose escalation, a licensed study clinician will call the subjects within 1 to 3 days after the dose escalation to determine whether the subject has experienced any clinically significant adverse effects. If the subject does not tolerate the increased dose, the subject may be instructed to either resume the 1 capsule dose or be discontinued from the trial, dependent on the judgement of the licensed clinician investigator. If the subject does not tolerate the 2 capsule dose at either or both Week 5 and Week 7, the subject will remain on the one capsule dose for the duration of the trial. If the dose escalation is tolerated at both Week 5 and Week 7, the dose escalation will be attempted again at the start of Weeks 9, 11, 13, and 15.

Since this is a double-blind study and it will not be known in which weeks the subject is being treated with MPH, these phone calls will occur twice during each block, at the start of the second and fourth weeks of the block. If the subject is being treated with MPH, this dose escalation will be from 18 mg MPH (1 capsule) to 36 mg MPH (2 capsules).

6.1.4 **Follow Up Visit- Week 18**

This visit will take place after 14 days ± 1 day following the Week 16 visit. The following procedures will be performed and will take approximately 1 hour.

- Assess and document adverse events (AEs)
- Review and document concomitant medications, supplements, and therapies
- Measure vital sign
- Perform ECG
- Debriefing with Investigator on subject's data during trial and experience in the study

6.1.5 **Early Discontinuation Visit**

The following procedures will be performed and will take approximately 2 hours.

- Assess and document adverse events (AEs)
- Review and document concomitant medications, supplements, and therapies
- Measure vital signs
- Perform ECG
- Administer neuropsychiatric assessment C-SSRS, GDS, ABID, BAI, AES, FAQ, and ADCS-MCI-ADL (24)
- Administer neurocognitive Assessments, including RBANS, CPT, Trails, and BVMT-R
- Assess drug accountability/compliance

6.1.6 **Missed Visits and Procedures**

Missed visits and any procedures not performed (not attempted) for reasons other than illness, injury, or progressive disability (i.e.: a subject is physically unable to perform them) will be reported as protocol deviations.
Procedures or visits not performed due to illness, injury, or disability, including procedures that were attempted but failed (i.e.: blood samples unable to be drawn after multiple attempts or weight unable to be obtained due to subject immobility) will not be reported as protocol deviations.

6.2 Clinical Assessments

Assessments will be performed at designated time-points throughout the study for clinical evaluation. In addition to the assessments evaluated below, subjects will provide information on their demographics, past medical history, including Alzheimer's Disease and Related Dementias (ADRD) history, family history, and medication usage.

6.2.1 Safety Measures

Assessments will include vital signs, ECG and AEs at all study visits and blood work at screening for hematologic and metabolic abnormalities that may confer risk of participation.

6.2.1.1 Vital Signs, Height, Weight

Vital signs, including systolic and diastolic blood pressure, temperature, and pulse rate (radial artery)/minute, will be assessed at specified visits using an at-home blood pressure cuff. Self-report height and weight will be documented at the Screening Visit. The subject will be asked to take their blood pressure, temperature, and pulse rate using an at-home monitor that will be sent to the subject as well as an oral thermometer. The Vital signs will be supervised by the study team and taken on camera during the study visit.

6.2.1.2 Blood Collection

Study participants will have blood drawn during the in-person screening visit or be asked to have a blood test at an off-site, certified blood draw facility after their virtual screening visit but before they are randomized. Participants will provide approximately 11 mL (approximately 2.5 teaspoons) of blood. Study funds will be used to pay for the tests. Study funds will not be used to reimburse subjects who have their blood drawn through an uncontracted lab facility. The participant will have his or her whole blood collected by either a nurse or phlebotomist from a peripheral vein. Blood will be handled, processed, and analyzed in accordance with regulations set forth by the American Society for Clinical Pathology and the College of American Pathologists.

6.2.1.2.1 Serum B12 and folate Testing

All participants will have their serum B12 and folate levels tested. Testing B12 requires 3.5 mL of blood collected intravenously from a peripheral vein of a study participant into an appropriate closed-top tube. Serum B12 and folate levels will be collected at the screening visit.

6.2.1.2.2 Serum Thyroid Stimulating Hormone Testing

All participants will have their thyroid stimulating hormone levels (TSH) tested. Testing TSH requires 3.5 mL of blood collected intravenously from a peripheral vein of a study participant into an appropriate closed-top tube. TSH levels will be collected at the screening visit.

6.2.1.2.3 Complete Blood Count with Differential Testing

A complete blood count and differential test will be conducted at screening. Testing for the CBC and differential requires 0.5 mL of blood collected intravenously from a peripheral vein of a study participant into an appropriate closed-top tube. A complete blood count with differential testing will include:

- Red blood cells
- Hemoglobin
- Hematocrit

- Mean corpuscular volume
- Red cell distribution width
- White blood cells
- Platelets
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

6.2.1.2.4 Complete Metabolic Panel Testing

All participants will have a complete metabolic panel test performed twice (screening visit and week 16.) This testing requires 0.4 mL of blood collected intravenously from a peripheral vein of a study participant into an appropriate closed-top tube. The complete metabolic panel test will include:

- albumin
- alkaline phosphatase
- alanine aminotransferase
- aspartate aminotransferase
- BUN
- Calcium
- Chloride
- Carbon dioxide
- creatinine
- glucose
- potassium
- sodium
- total bilirubin
- total protein

6.2.1.3 Columbia Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale (C-SSRS) (34) will be performed at every visit per the recommendations of the US FDA to monitor suicidality. At the Screening Visit, The Screening Version will be used while the Since Last Visit Version will be administered at all other visits. Prior to the administration of this measure, the complete address of the site they are utilizing to complete the visit (e.g. home address, including apartment/unit number), the participant's phone number, and an additional contact number, will be recorded. Should the participant endorse active suicidal ideation and plan, or display behaviors indicative of potential self-harm, with a response of "Yes" to Question 4 or 5 of the C-SSRS or any spontaneous expression of suicidality (i.e., behavior that places themselves at imminent risk of injury or death, including verbal threats to self-harm, self-destructive behaviors or potentially lethal suicidal acts), will result in emergent evaluation by a licensed clinician member of the study staff for appropriate assessment and triage.

6.2.1.4 6-Lead ECG

A standard 6-lead ECG and rhythm strip will be performed at each visit using the KardiaMobile 6L, an FDA-cleared personal ECG device and the KardiaMobile software platform (Figure 3). To use the KardiaMobile 6L,

subjects must put their fingers on the silver electrodes and touch the back of the device to the bare skin of their left leg. The device records 30 seconds of ECG data that is shown on a smartphone or tablet via the KardiaPro software. Tracings will be downloaded from the KardiaPro database, reviewed by a trained clinician investigator, and stored in the subject binder as part of the source documentation. If during the first 8 weeks, there are no clinically significant abnormalities or changes in the ECGs, ECGs will not be done at the remainder of the Crossover Visits. If new cardiac compliant occurs, ECGs will be resumed. If the ECG performed at the visit displays a new abnormality, we may ask the subject to have an additional 12-lead ECG in person, either at the office at the Charlestown Navy Yard or an off-site certified lab facility.

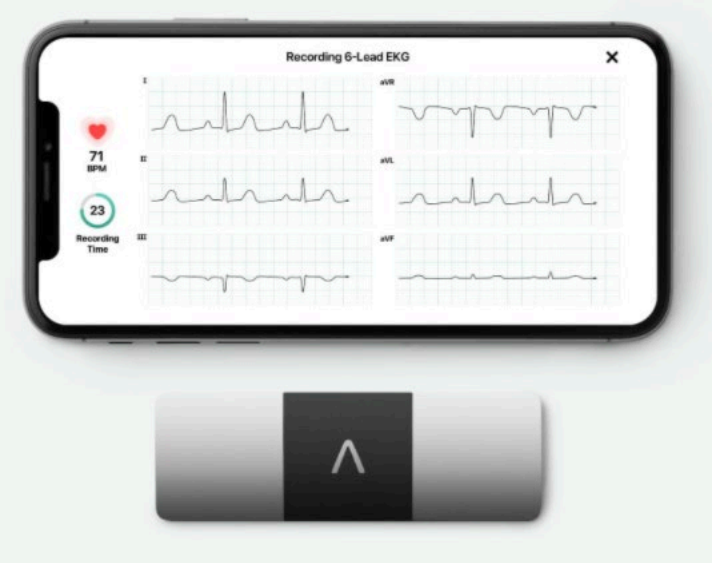


Figure 3. KardiaPro ECG example and KardiaMobile 6L Device.

6.2.1.5 Adverse Events

Once the informed consent form has been signed by the subject, inquiry about all adverse events (AEs) will be performed at each study visit.

6.2.2 **Neurocognitive Assessments**

6.2.2.1 Montreal Cognitive Assessment (MoCA) (35)

Montreal Cognitive Assessment (MoCA) is a commonly used screening tool in clinical trials and research settings to measure levels of cognitive impairment. The MoCA measures five areas of cognitive function: orientation, visuospatial, attention and calculation, recall, and language. The MoCA will take approximately 10 minutes to complete and will be administered by experienced raters following the virtual administration recommendations specified by the test publishers.

6.2.2.2 Repeatable Battery for the Assessment of Neuropsychological Status Update (RBANS)

The RBANS (36) is a commonly used 25-minute, standardized neurocognitive battery with four parallel versions, making it particularly suitable for repeat assessments to control for practice effects. The RBANS measures five neurocognitive domains, with twelve subtests consisting of with immediate memory (List Learning and Story

Memory), visuospatial/constructional (Figure Copy and Line Orientation), language (Picture naming and Semantic Fluency), attention (Digit Span and Coding), and delayed memory (List Recall, List Recognition, Story Memory, and Figure Recall). The RBANS is extensively used in clinical trials and has been shown to be effective at both detecting and characterizing forms of dementia as well as tracking progression or response to treatment in neurological disorders. The Delayed Memory domain has been shown to be particularly sensitive to discriminating mild cognitive impairment (MCI) due to Alzheimer's disease from controls, and also is predictive of cerebral amyloid burden (36). The RBANS will be administered virtually. The coding subtest response form will be mailed to subjects before their scheduled visits along with a prepaid envelope for the form to be returned.

6.2.2.3 Millisecond Continuous Performance Test (CPT)

(37)The AX Continuous Performance Test (37) is a test of sustained attention (vigilance) and inhibitory control in which subjects are visually presented with a string of letters appearing one at a time on a screen. For the first part of the assessment, the subject is instructed to press a button every time they see an "X" and not to press it for any other letter for a span of five minutes. The subject is then given a brief break before continuing to the next part of the study, the AX task, which is a measure of inhibition and executive control. In this section, the subject is told to press the button when they see an "X" that immediately follows the letter "A" but not when there is an "X" that is not preceded by the letter "A". This second task block also lasts for five minutes. Task administration will utilize Millisecond Inquisit Web software, a stimulus presentation platform optimized for temporally precise stimuli presentation and reaction time recording of digitized psychological assessments. Inquisit Web requires only a subject code and no personally identifiable information.

6.2.2.4 Brief Visual Memory Task-Revised (BVMT-R)

The BVMT-R (38) is a test of visuospatial memory with six equivalent alternate forms. The BVMT-R has three learning trials, a 25-minute delay, and then delayed recall and recognition trials. The presentation of the visual stimuli will be presented digitally via videoconferencing. The recall and recognition portion of this assessment will be given in the traditional, pencil and paper format and scored according to published administration instructions and norms. Permission to adapt BVMT-R stimuli into a digital format was granted by the publisher of the test.

6.2.2.5 Narrative Speech Production Task

Illustrated line-drawings depicting various semantically rich scenes will be presented to subjects to elicit narrative speech generation. Task stimuli will utilize scenes from Highlights Magazine-Hidden Picture activity worksheets where subjects will be asked to describe what is occurring in the scene. Each subject's narrative discourse of the scene will be digitally recorded in order to analyze speech rate and rhythm and to provide information on the subject's semantic knowledge and productive fluency**.** Highlights magazine is a children's magazine, and scenes will be selected from Highlights Hidden Picture 4-book set purchased specifically for study use. The subjects will be presented with a different scene at each study visit for a total of eight scenes across eight visits.

After the scene description, participants will be asked to perform additional speech production control tasks as a baseline measure of speech production, processing speed, attention, and working memory. Tasks include the Repeated Consonants task and the Months Forward and Backward Test (39). The Repeated Consonants task, in which the subject is asked to repeat 3 syllables ("la", "ga", and "ma"), is primarily used to calibrate the speech production analysis. In the Months Forward and Backward Test task, the subject is asked to recite the months of the year first in forwards order and then asked to recite them in backwards order. This measure is quickly

administered, taking less than five minutes, yet it is quite sensitive to cognitive dysfunction (83-93% sensitivity for detecting neurocognitive dysfunction). The assessment is scored on a scale from zero to one for both Forwards and Backwards subtests, with a score of zero indicating an inability to complete the task or an error in recitation. Similar to the narrative speech task, each subject's oral generation of months forward and backward will be digitally recorded in order to analyze speech rate, rhythm, and fluency.

Speech tasks will be administered and recorded using the web-based SurveyLex data collection software. Subjects will be sent a link to a speech survey that will guide them through the various tasks. Subjects will press 'record' buttons within the survey to provide their responses. Study coordinators will be on the Zoom call while the subject is completing these tasks for assistance.

6.2.2.6 Trial Making Test

The Trail-Making Test (40) is a graphomotor letter and number-letter sequencing task that will be administered to test processing speed, mental flexibility, and set-switching. The standard, paper version of this test cannot be administered virtually, so the oral Trail Making Test (41) will be used instead. The test takes approximately 5 minutes to complete, and it will be administered at all block visits.

6.2.3 **Neuropsychiatric Assessments**

All neuropsychiatric questionnaires will be administered over Zoom videoconferencing.

6.2.3.1 Neuropsychiatric Inventory Questionnaire (NPIQ)

The Neuropsychiatric Inventory – Questionnaire examines 12 sub-domains of behavioral functioning including: hallucinations, delusions, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, eating abnormalities, and night-time behavioral alternations. The NPI-Q is completed by a trained rater through interview with the subject's study partner. It is well-validated and extensively used in clinical trials in AD. The NPI-Q will be administered at screening to determine subject eligibility and will require an answer of "No" on question 4, which inquiries about symptoms of agitation or aggression that could worsen due to treatment with MPH.

6.2.3.2 Geriatric Depression Scale (GDS)

The GDS (42) is a questionnaire designed to identify and quantify the presence of depression in the elderly. The scale consists of 15 yes/no questions related to how the subject has felt over the previous week and take approximately five minutes to administer. The GDS includes items to which positive and negative answers are indicative of a symptom of depression. One point is given for each such appropriate answer, with a possible total of 15 points. Total scores of zero to five are considered normal and scores of six to 15 are considered indicative of depression. A GDS less than seven is required for inclusion in the study.

6.2.3.3 Apathy Evaluation Scale (AES)

The Apathy Evaluation Scale (43) is comprised of two 18-item subscales: the subject's self-report and an informant report that each take about five minutes to complete. The scale assesses affective, cognitive, and behavioral measures of apathy and asks the user to rank how much the subject experiences each item (zero being not at all and a four being frequently). A lower score indicates greater apathy.

6.2.3.4 Beck Anxiety Inventory (BAI)

The BAI (44) is a 21-item, self-administered questionnaire that measures the presence and severity of anxiety in psychiatric populations. It was constructed to avoid confounds due to comorbidity of depression, and it has been

found to be highly valid, reliable, and consistent. The BAI lists 21 common symptoms of anxiety and asks the subject to rate the severity with which they experience each symptom (not at all, mildly, moderately, or severely). Scores of 0-21, 21-35, or 36-63 indicate low, moderate, or severe anxiety respectively.

6.2.3.5 The Aggressive Behavior in Dementia Scale (ABID)

The ABID (45) is a scale designed specifically for use in mild to moderate Alzheimer's populations. It is a caregiver-administered scale that takes about 5 minutes to complete. It evaluates frequency of 16 observable, agitated behaviors that are commonly problematic in mild to moderate AD and asks the caregiver to rate their level of distress about each behavior. This results in summed total score for the behaviors and caregiver distress, with a higher score indicating more agitation and distress due to agitated behaviors. It has been shown to be a reliable and valid evaluation of both frequency of and reaction to agitated behaviors in dementia.

6.2.4 **Functional Assessments**

All neuropsychiatric questionnaires will be administered over Zoom videoconferencing.

6.2.4.1 Functional Activities Questionnaire (FAQ)

The FAQ (46,47) is a brief informant-administered rating scale used to determine a subjects' level of functional independence when performing a range of instrumental activities of daily living (IADLs), with repeat assessments useful for monitoring performance in these areas over time. The FAQ total score (ranging from 0-30) reflects the sum of ordinal ratings (0 = fully independent, 1 = has difficulty but does by self, 2 = requires assistance, and 3 = dependent) across ten items assessing a variety of functional activities (i.e., preparing a balanced meal, financial management skills, and shopping), with higher scores indicating increasing levels of dependence. For activities not normally undertaken by a person, a score of 1 is assigned if the informant believes the subject would be unable to complete the task if required, or a score of 0 is assigned if the informant believes the subject could successfully carry out the task if needed. Overall, the FAQ is a sensitive marker of functional impairment among individuals with varying dementia severity and has been shown to differentiate mild cognitive impairment from early Alzheimer's Disease with 80% sensitivity and 87% specificity. The FAQ demonstrates high reliability (exceeding 0.90), takes about five minutes to complete, and requires limited rater training to administer. The FAQ will be administered at each study visit.

6.2.4.2 Alzheimer's Disease Cooperative Studies-Activities of Daily Living Scale-Mild Cognitive Impairment (ADCS-ADL- MCI) (24)

The ADCS-ADL-MCI (24) (48) assesses the subject's ability to complete activities of daily living through a 24-item study-partner based assessment. It assesses areas such as eating, bathing, grooming, cooking, household, chores, shopping, keeping appointments, social interactions and hobbies. The study partner is asked whether the subject has performed the task within the past 4 weeks, and if so, what level of assistance the subject required (independently, with supervision, or with physical help). Scores range from 0 to 69, with lower scores indicating more impairment. The scale has been tested and verified across varying severities of AD and has been shown to be sensitive to drug effects in clinical trials (49).

6.2.4.3 Dementia Severity Rating Scale (DSRS)

The DSRS (50) is a brief 12-item questionnaire administered to an informant that assesses a subjects' functional abilities and offers a global characterization of everyday activities that may be impacted by neurodegenerative disease. The DSRS is designed in a multi-choice format with strong concurrent validity and parallel content to material covered on the Clinical Dementia Rating Scale (CDR), a commonly employed dementia staging

instrument46. The DSRS is a highly reliable scale with an intra-class correlation of >90% for interrater reliability and Cronbach's alpha > 0.70 for internal consistency and has been shown to accurately discriminate between cognitive healthy individuals and dementia subjects of varying severity. Further, the DSRS allows for a broad range of scores (total score 0-54) making it suitable to quantify a wide range of functional impairment without being hampered by floor effects seen in more advanced disease, while also making it sensitive to detecting incremental change in functional ability over time. The DSRS takes about five minutes to administer, requires minimal rater training, and can be administered over the phone to study subjects if required.

6.3 Daily Outcomes

6.3.1 **Mood and sleep ratings**

Before beginning each Lumosity session, the subject will be asked to rate their mood, sleep, and overall well-being each day. The survey will require no more than 3 minutes of the subject's time.

6.3.2 **Cognitive exercises**

Each subject will be provided with a Lumosity account. The subjects will be required to complete 6 different cognitive exercises (about 10-15 minutes) 6 days per week for the duration of the study (from Week 0 to 16). The assigned cognitive assessments will sample the domains of attention, processing speed, memory, cognitive flexibility, and problem solving. Compliance will be assessed weekly by the study coordinator by logging on to each subject's Lumosity account. If the subject is not adhering to the cognitive exercise requirements, the study coordinator will contact the subject or their study partner to remind them of proper exercise procedures. If a subject requires more than three such reminders, they will be considered non-compliant, and PI will determine if the subject should continue in the study or if their study participation should be discontinued.

6.3.3 **Daily activity and sleep tracking**

Each subject will be provided with a Fitbit Charge 3 that they will wear throughout the study. The device will track the participant's heart rate, activity, and sleep. The subject will be instructed to wear their device at all times except for when it is being charged.

6.3.3.1 Charging and syncing procedures

Subjects will be instructed to ensure that the device is charged at all times. The subject will be instructed to charge their device about once every 4 days during a period of inactivity, such as when watching TV or reading. The subject will be explicitly instructed not to charge their device during times of sleep. The subject will be instructed to sync their device before or after their daily Lumosity games. Charging and syncing compliance will be routinely monitored by a study coordinator. The coordinator will conduct reviews of the subject's charging and syncing compliance by logging onto the subject's Fitbit dashboard. If the device has not been appropriately charged or synced, the study coordinator will contact the subject or their study partner to remind them to sync or charge their device as needed. If a subject requires more than three such reminders throughout the duration of the study, the subject will be considered non-compliant, and the PI will determine if the subject should continue in the study or if their study participation should be discontinued.

6.4 Training and Validation

All evaluators must be trained and approved by the study neuropsychologist to perform cognitive and psychiatric outcome assessments. It is strongly preferred that a single evaluator performs all measures with a given instrument throughout the study when possible.

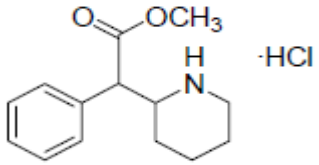
6.5 Treatments Administered

6.5.1 Treatments

6.5.1.1 Study Product Description (22)

The form of MPH administered to subjects is CONCERTA® or generic, d,1 (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride ($C_{14}H_{19}NO_2$•HCl). It is a white, odorless crystalline powder.

6.5.1.2 Chemical Structure of CONCERTA®:



Concerta® is an extended-release form of MPH that minimizes fluctuations between peak and trough concentrations of immediate release MPH taken in multiple doses per day while providing comparable bioavailability.

6.5.1.3 Drug and Placebo

Concerta® or equivalent generic extended release MPH 18 mg will be over encapsulated in a gelatin capsule with inert filler by the MGH Research Pharmacy. Identical-appearing capsules with only filler will be prepared as placebos.

6.5.2 Acquisition

The study drug will be picked up from the MGH Clinical Trials Pharmacy by a study coordinator. The study drug will be picked up from MGH Clinical Trials Pharmacy on the same day it will be shipped to the participant via mail or a courier. The drug will be sent per the recommendations of MGH Clinical Trials Pharmacy. We will confirm that the subject will be at home at the scheduled delivery time so that they are able to sign for the drug upon its arrival.

6.5.3 Product Storage and Stability

Extended release MPH/Placebo should be stored at 25°C, with excursions of 15-30°C and should not be stored at high humidity. The maximum use by date is 6 months. No drugs will be stored in the research clinic. Any drug returned by the subject will be destroyed the same day using the Medline Drug Buster drug disposal system.

6.5.4 Dosage

Extended release MPH/Placebo should be taken orally once daily in the morning with or without food. The tablet capsule must be swallowed whole and must not be chewed, divided, or crushed. Subjects will take 1 capsule of MPH for the first week of each block. If the 1 capsule dose is tolerated, the subject's dose will be increased to 2 capsules of MPH for the second week of each block. To determine safety of a dose escalation, a licensed study

clinician will call the subjects to determine whether the subject has experienced any clinically significant adverse effects. Safety phone calls will occur before and after dose escalation (see Section 6.1.3.1) If the subject continues to tolerate the 2 capsules during Block 1, then they will be escalated on Blocks 2 and 3. If the subject does not tolerate the 2 capsules dose, they will remain on the 1 capsule for the duration of the trial.

6.5.5 **Modification of Study Drug for a Subject**

Dosing may be suspended or decreased at any time by the PI or designated licensed clinician sub-investigator. This will be documented along with the reason(s) and dates of adjustment in the CRF for each subject requiring this manipulation. The PI or designated licensed clinician Sub-Investigator may decrease or suspend the dosage of study drug or discontinue the study drug for AEs thought to be related to the study drug or for other reasons during the trial (the reason and dates of dose reduction or suspension must be documented in CRF). If the AE is mild or moderate, the dosage may be re-started after the event improves. If the AE is serious or life threatening, and deemed to be definitely related to drug, the study drug will be discontinued immediately. Study subjects must remain off the study drug permanently. Subjects may not resume study drug. All AEs will be followed to resolution. The dose will not be escalated to greater than 36 mg without IRB approval

6.5.6 **Dosage Discontinuation**

Reasons for discontinuation of study medication may include an AE or PI recommendation, protocol deviation, loss-to-follow-up, patient request, or death. All serious adverse events (SAEs) that occur in a subject who has discontinued early must be recorded and reported within 24-hours of awareness. Study subjects who discontinue study drug prematurely (early discontinuation from study) and decide not to remain in the study will be encouraged to return for an Early Discontinuation Accountability Visit.

6.5.7 **Assessment of Subject Compliance**

Subjects will be dispensed enough pills to get them to the next drug dispense. At each virtual visit, subjects will be asked to show each their pill bottles on camera to display any unused study medications. If the subject does have unused study medication, it will be sent back to the study team for destruction. Research staff will review returned and unused study medication and log in drug reconciliation form to determine compliance. Non-compliance will be defined as taking less than 80% or more than 125% of study medication as determined by unused capsule counts. If a study subject is non-compliant with study medication, research staff should re-educate and train the subject in administration of study drug. If the subject's non-compliance persists, it will be left up to the PI to determine whether the subject should be discontinued from the study.

6.5.8 **Contraindications and Warnings**

6.5.8.1 Prohibited Medications (22)

Concurrent treatment with Monoamine Oxidase Inhibitor (MAOI) antidepressants or discontinuation of an MAOI within 14 days of the baseline visit.

Because of possible increases in blood pressure MPH should be used cautiously with vasopressor agents. MPH may also inhibit the metabolism of coumadin, phenobarbital, phenytoin, primidone, and tricyclic antidepressants, so subjects requiring these medications will be excluded. It may be necessary to adjust the dosage and monitor plasma drug concentrations when using MPH concurrently.

6.5.8.2 Contraindications

MPH is contraindicated for use in patients with marked anxiety and agitation, as MPH may worsen these symptoms. It is also contraindicated in patients with motor tics, glaucoma, a diagnosis or family history of Tourette's Syndrome and in those patients with a hypersensitivity to MPH.

6.5.8.3 Warnings

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at doses for ADHD treatment, but the role of the stimulant in these events is unknown. Adults with significant cardiac conditions such as structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems should avoid being treated with stimulant drugs. MPH should be used with caution in subjects with hypertension or other cardiovascular conditions, as it has can increases in blood pressure by 2-4 mmHg and average heart rate by 3-6 bpm. Particular caution should be used in patients with conditions such as pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

MPH should be used with caution in subjects taking vasopressor/hypertension medications. MPH has also been shown to reduce the effectiveness of anticoagulants, anticonvulsants, tricyclic drugs, and decongestants.

Treatment with MPH may exacerbate pre-existing psychiatric conditions or possibly cause the emergence of new psychotic or manic symptoms. Stimulants have also lower the convulsive threshold in patients with history of seizures and EEG abnormalities without seizures. Some patients have also reported blurring and accommodation of vision with stimulant use.

MPH should be used with caution in patients with a history of drug dependence or alcoholism, as long-term use could lead to psychological dependence.

6.6 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trials protocol, Good Clinical Practice (GCP). The noncompliance may be either on the part of the subject, the SI or the study site staff. In the event of deviations, corrective actions are to be developed by the site in conjunction with the coordinating team and implemented promptly. All deviations from the protocol must be addressed in the subject's source documents. Protocol deviations must be sent to the local IRB per the guidelines and entered in the Protocol Deviations Log in the EDC system

7 BIOSTATISTICAL ANALYSIS

This is a small-scale pilot study using a multi-crossover randomized controlled trial (MCRCT) design that is novel in the field of neurodegenerative dementias. Its goals are two-fold: 1) to obtain descriptive data on the effects of a potential cognition-enhancing drug for symptomatic treatment of MCI and mild-stage dementia; and 2) to evaluate feasibility, time, cost, acceptability of an array of methods and instruments for participants that will allow us to refine methods, estimate adequate power and improve upon the study design prior to performance of a full-scale research project with MPH and other potential cognition-enhancing drugs using similar designs and methods.

Primary feasibility outcomes will include measures of retention, adherence/compliance, and safety. Study protocol compliance will be based on completion rates for each of the outcome measures described in this trial, which will subsequently be combined across participants to form 95% confidence intervals for each outcome. Medication

compliance will be determined based on each participant's pill reconciliation conducted between each block, and subsequently combined across all participants to generate a measure of overall medication compliance. Study retention will be assessed using completion rates of all participants enrolled in this pilot. Finally, we will collect qualitative feedback from each participant throughout the trial and upon study completion (or early termination) to assess their opinions on the tolerability and acceptability of the MCRCT design and the various study tasks. Areas of particular interest will include duration of study participation, frequency of assessments, ability to navigate all study technology, use of the virtual platform, and overall burden of daily assessments.

In this study, the participants will pass through three blocks of treatment with both MPH and PBO for two weeks each, administered in random order for each block. Our primary cognitive outcome measure will be the Total Scale score of the RBANS which will be administered at baseline, each crossover and end of study. The RBANS is a robust 25-minute, standardized neurocognitive battery with multiple versions whose 12 subtests yield five Index scores for each cognitive domain and the Total Scale score. Normative data have been published for cognitively normal older adults, MCI and AD. For example, In a study of MCI, the mean Total Score was reported to be 92.4 with a standard deviation of 9.1 (51). Based on test-retest reliability, a minimal detectable change in community-dwelling older adults (including normal, MCI and mild dementia) for the Total Score of 5 (52). A "minimum clinically important difference" in MCI was reported to be 8 points (53).

The basic data of a MCRCT are the measurements obtained in two or more different treatment conditions occurring repeatedly over time. The principal goal is to compare outcomes for each condition within a randomized block structure while accommodating repetition within subjects and possible effects of carryover or disease progression. Statistical methods used in MCRCTs include visual inspection of outcomes, aggregated t-tests, mixed effects longitudinal modeling, and Bayesian analysis. Similar but more complex mixed effects longitudinal models could accommodate carryover effects and time trends in settings in which the block lengths are longer than temporal effects so that they are not washed out in the comparison of treatments within blocks.

Data analysis at the individual level (N-of-1) for the primary outcome will begin with visual inspection of RBANS Total Scores at each assessment for differences from baseline for each measurement and differences between treatment conditions within each block. Ignoring potential for carryover, a simple matched pair t-test will be performed using data from each condition in the three blocks. Should carryover effects or other time trends be suspected, we can use a regression model adjusting for block and sequence.

We will also pilot aggregated/combined analysis of data. Individuals' MCRCT data will be combined using a multilevel random effects model that incorporates variance within and between participants. This within-patient level will accommodate variation resulting from the treatment crossovers as well as time effects modeled in various forms (e.g., linear and non-linear trends, carryover effects). Each within-subject regression coefficient will be treated as a random effect that can vary based on these between participant factors. The primary analysis will calculate the average treatment effect (i.e., will model the mean of the individual treatment effects as a constant). Secondary analyses will model the mean as a function of factors that vary among patients such as age and sex. These terms describe the main effects of these factors, their interactions with the treatment, and their interaction with time.

The full multilevel model will estimate both average effects across the population of participants, as well as effects for individuals informed by the results on other participants. The predicted effects for an individual participant are weighted averages of his or her data and the averages from others. This model incorporates

correlations among the measurements within an individual and enables comparison of the individual's predicted treatment effect using the multilevel model with that from using only that individual's data.

Carryover is always a risk in crossover studies. While MPH half-life is short, and the two-week duration of treatment for PBO should allow complete washout of MPH pharmacological effect, we cannot exclude carryover and practice effects affecting measures in successive assessments. We do not expect carryover pharmacological effects from PBO, but carryover might differentially affect measurements made in an MPH treatment period that follows another MPH treatment period. This may be difficult to gauge with our primary RBANS outcome measure taken only once at the beginning/end of each treatment period. However, we will have other resources with which to evaluate this using our exploratory outcomes, especially the daily cognition measures. We will investigate various adjustments for carryover, such as discarding the first measurements in a treatment period on outcomes measured daily, to determine whether results are sensitive to carryover. These adjustments can allow for potential differential carryover by treatment regimen. Bayesian models can be estimated using Markov chain Monte Carlo with model assessment using posterior predictive checks and the deviance information criterion. Non-Bayesian models can be fit using generalized linear and nonlinear mixed models.

8 RISKS AND DISCOMFORTS

8.1 MPH Side Effects

Common side effects include headache, stomach ache, trouble sleeping, decreased appetite, nervousness, and dizziness. More severe side effects have also been reported, including heart-related and psychiatric problems. See Section 6.5.8 for details.

8.2 Phlebotomy for safety labs

The risks associated with having blood drawn include bruising and local discomfort. Rarely an infection may occur at this site, and if an infection does occur it will be assessed and treated by the study physician.

8.3 Neurocognitive testing

The neurocognitive tests that will be administered to assess mental performance may be stressful and potentially cause anxiety, fatigue, and frustration. In our prior experience with similar protocols, risks have occurred infrequently and very few subjects have terminated testing. However, testing will be discontinued immediately upon any request by the subject to do so.

8.4 Neuropsychiatric and Functional Questionnaires

Questionnaires administered during the protocol may cause subjects to feel sad or upset about their diagnosis and daily functioning or how it affects their quality of life. Study staff is experienced with such evaluations and sensitive to these issues. Any question can be omitted per the subject's request.

8.5 Daily cognitive exercises

The daily Lumosity may be stressful, tedious, and potentially cause fatigue and frustration. However, because the Lumosity program was designed to resemble games and the duration of exercises is short, we believe that the likelihood of these risks is low.

8.6 Wrist Actigraph

The wrist actigraph, the Fitbit Charge 3, may cause some minor discomfort due to prolonged wearing, but the risk of such discomfort will be minimized by ensuring the wristband fits the subject properly (e.g. is not too tight or does not cause irritation).

8.7 Data security

8.7.1 Laptop computers

Subjects will be given the choice to use their personal computers or study-provided laptops to use for Lumosity cognitive exercises and Fitbit activity tracking. Fitbit and Lumosity are web-based applications that require no PHI or personally identifiable information be entered into the system, so there are no additional data safety risks to the subject if they use their personal computers. Older adults may have difficulty adapting to new technologies, resulting in increased cognitive and perceptual demands(54). Because a major outcome of this trial is performance on computerized cognitive brain games, it is important that subjects' performance is not influenced by the novelty of the study laptop.

If a subject does not wish to use their personal computer, they will be provided with a study laptop. Study laptop computers will be registered under the Principal Investigator and no identifying information will be required to sign in. The study subject will be provided with a password that adheres to Partners password requirements to log in to the computer. We will also provide an information sheet with detailed instructions on how to use the laptop to complete study tasks.

Subjects will be given laptops to use for Lumosity cognitive exercises and Fitbit activity tracking. Lab laptop will be registered under the Principal Investigator and no identifying information will be required to sign in. The study subject will be provided with a password that adheres to Partners password requirements to log in to the computer. We will also provide an information sheet with detailed instructions on how to use the laptop to complete study tasks.

8.7.2 Study Visit Recording

Audio will be recorded during the speech production tasks for data collection and analysis purposes. Audio will be recorded using SurveyLex online surveys only during the speech production task. The audio data files will be deidentified. This data will be sent to a commercial server (for example, Amazon Web Services). This is necessary to ensure that large quantities of data are safely backed up and organized. The data will be subsequently transferred to secure Partners databases. All communications with the server will be done via SSL for secure transfer. The data collected in this manner does not include identifiable information such as name, DOB, or MRN. The only information passed into this application is the deidentified study identification number assigned to the participant and their age.

8.7.3 Lumosity software

For the successful completion of this research study, Lumosity will provide de-identified user accounts to Dr. Arnold. The research team at MGH will be responsible for assigning these de-identified accounts to research participants, as they are enrolled in the trial. These accounts will have a generic date of and will not contain any personal health information or personally identifying information. Lumosity does not collect or store any personally identifying information of research participants. A copy of Lumosity's Privacy Policy and Terms of

Service will also be reviewed by the subject during the consenting process. By consenting to the study, the subject is also agreeing to these policies and terms.

Any record of cognitive exercises and assessment data provided by Lumos Labs to MGH will be restricted to data created through or generated by study subjects or study subjects access to or use of Lumosity and will not contain personal information of other Lumosity users. Lumos Labs will send data reports via email to the study staff in a CSV file which will be downloaded and stored on Partners compliant workstations.

8.7.4 **Fitbit activity tracker (55)**

A study coordinator will create a unique, deidentified email and password combination to create an account on Fitbit.com. To create an account, the following information will be required: first and last Name (a de-identified placeholder name], date of birth (January 01, year of birth), gender, height, and weight. The subject will be given the associated account information so that they are able to login, sync their device, and use the Fitbit dashboard. The subject will be notified that the researcher will also have full access to their account and will be able to freely view and download the subject's data for research purposes. A copy of Fitbit's Privacy Policy and Terms of Service will also be reviewed by the subject during the consenting process. By consenting to the study, the subject is also agreeing to these policies and terms.

After the subject has completed or if they are withdrawn from the study, their Fitbit account and all associated data will be deleted. However, prior to deleting the account, the de-identified study data will be downloaded and stored confidentially on Partner's computers for study purposes.

8.7.5 **ECG**

ECG testing will be done at every visit Subjects will perform their own ECG at home using the KardiaPro software and KardiaMobile 6L device. KardiaPro is a medical-grade ECG recording system produced by AliveCor, Inc. This platform does not require any PHI. The study ID is the only identifiable information that is required to be entered. This application can be downloaded to subjects' personal smartphone. If the subject does not have a smartphone, they will be provided with a study iPad to use with their KardiaMobile device. The KardiaPro app is encrypted and highly secure.

8.7.6 **iPad**

If subjects do not want to use their personal smartphones for the KardiaPro applications, subjects will be given iPads to access the application. iPads will be registered under the Principal Investigator and no identifying information will be required to sign in. The study subject will be provided the 6-digit passcode to log in to the iPad.

8.8 Other Risks

Reviewing health-related information might be stressful or make the subject feel uncomfortable. Subjects do not have to answer any questions they do not want to. In addition, there may be incidental medical findings as a result of the physical examination. If there is an incidental medical finding, a study physician or licensed nurse practitioner will review the results. If the study physician or licensed nurse practitioner believes that the finding may indicate a problem, the subject will be informed, and the study physician and licensed nurse practitioner will discuss next steps with the subject and help the subject arrange follow-up care for the problem. If the study physician or licensed

nurse practitioner thinks that the subject may have a medical problem, but it turns out that they do not, the subject may have been caused worry needlessly.

8.9 Potential benefits

MPH may improve cognitive and behavioral functioning in MCI and ADRD. If successful, this trial will allow further clinical development of use of MPH for the treatment of AD. The trial is also assessing daily cognitive abilities in concert with clinical outcomes, which will provide a detailed understanding of drug activity and provide a well-curated data set for the dementia research community to improve our understanding of ADRD.

This trial could contribute to the reshaping of clinical trial conduct by helping to understand the reliability and validity of using daily cognitive exercise measures as an alternative for standard neuropsychological assessments. This study has the potential to establish these daily cognitive tasks as a reliable tool for measuring cognitive performance. Additionally, the multi-crossover "N of 1" design has the potential to deliver more individualized treatment options for AD patients and improve future clinical trial conduct.

Feedback on the cognitive and clinical measures during the MPH vs placebo treatment periods will be offered to the subjects at the follow-up visit. They may be encouraged to discuss this feedback with their healthcare provides as it could inform further treatment options for their condition.

9 MONITORING AND QUALITY ASSURANCE

9.1 Independent monitoring of source data

The PI will ultimately be responsible for the validity and integrity of the data collected at the MGH site, and for ensuring that the study is conducted in accordance with the IRB-approved protocol. After data is collected and recorded on forms, the study coordinator may input the data into the Partners approved REDCap EDC. Entries will be reviewed for accuracy and completeness by a second study coordinator. Finally, the PI or his designee (Co-I) will conduct monthly reviews to check that data in REDCap accurately reflects the data collected on the original data capture forms. The research team (PI, Co-I, research coordinators) will subsequently meet to discuss the results of this review, as well as case report forms and source documentation.

All electronic documentation will be stored on password-protected devices in locked cabinets located in secured areas. Paper forms will be stored in locked cabinets located in secured areas.

Source documents that are sent to the subject (i.e. informed consent documents, cognitive testing materials) will be mailed back to the study team. To ensure validity of source documentation, the subject or study partner will put the documents into the envelope, seal the envelope, and sign the back of the envelope during the virtual visit.

9.2 Safety monitoring

The adverse event (AE) definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Conference on Harmonization (ICH) guidelines. The PI will carefully monitor each subject throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It will be important to report all AEs, whether serious or non-serious.

9.3 Adverse event reporting guidelines

9.3.1 Adverse Event

An adverse event (AE) is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device, whether or not considered related to the drug product or device.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc.), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (e.g. arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity are considered as worsened and therefore would be recorded as adverse events. Adverse events are generally detected in two ways:

- Clinical → symptoms reported by the subject or signs detected on examination.
- Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by a clinician investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by a clinician investigator.

Subjects will be monitored for adverse events from the time they sign consent until completion of their participation in the study (defined as death, consent withdrawal, loss to follow up, early study termination for other reasons, or following completion of the entire study). An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current Investigator's Brochure.

The study procedures and the well-being of all participants will be monitored closely by the Principal Investigator, Steven Arnold MD, and clinician Co-Investigators. Throughout the course of the study, constant feedback with the subject is maintained in order to assess comfort and safety and to minimize risks throughout the procedure. The above investigators will be responsible for determining if a subject should be removed from the study. Criteria for removal include the following: 1) if a subject is unwilling or unable to participate in study procedures 2) if the subject refuses to participate and consent, 3) if the subject acquires a medical condition that prohibits further participation, 4) if in the opinion of the MGH principal investigator, Dr. Steven Arnold, it is decided that it is not in the subject's best interest to continue participation.

Unanticipated problems including adverse events will be reported to the PHRC as described in the PHRC policy on Unanticipated Problems Involving Risks to Subjects or Others including adverse events.

The Data Management (DM) team will be responsible for the development, execution, and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets. All data will be managed in compliance with applicable regulatory requirements. The study coordinator, under the supervision of the PI, will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and/or other forms used to report, track, and record clinical research data. The study coordinator will be instructed to enter this information into the REDCap Electronic Data Capture (EDC) System. The REDCap platform provides password protection. An edit checking and data clarification process will be put in place to ensure accuracy of the data. Logic and range checks as well as more sophisticated rules may be built into the eCRFs to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing, or not calculated correctly. The platform will have the ability to lock specific visits to prevent any modification of data once the visit is closed. Once this option is activated, every user will have Read-Only access to the data. The PI, Dr. Arnold, will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

9.3.1.1 Serious Adverse Events

All adverse events will be reviewed by the Principal Investigator, Dr. Steven Arnold, and will be reported to Partners IRB and to the Human Research Committee (HRC) in accordance with HRC Guidelines. A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurs.
    - This serious criterion applies if the study subject, in the view of the PI, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    - Hospitalization for an elective procedure or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.
    - This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the subject’s ability to carry out normal life functions.
5. Results in congenital anomaly or birth defect in the offspring of the subject.
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience and will therefore not be considered an SAE. An example of this would include a social admission (subject admitted for reasons other than medical, e.g., lives far from the hospital, has no place to sleep).

The PI is responsible for classifying adverse events as serious or non-serious. If the PI is not available to assess seriousness within 24 hours, a clinician investigator will assess seriousness and speak with the PI at the soonest time they are available.

9.3.2 **Assessment and Recording of Adverse Events**

The PI will carefully monitor each subject throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be collected and reported in the EDC system.

9.3.3 **Assessment of Adverse Events**

At each visit (including telephone visits), the subject will be asked if they had any problems or symptoms since their last visit in order to determine the occurrence of adverse events. If the subject reports an adverse event, the Investigator will probe further to determine:

- Type of event
- Date of onset and resolution (duration)
- Severity (mild, moderate, severe)
- Seriousness (does the event meet the above definition for an SAE)
- Causality, relation to investigational protocol
- Outcome

9.3.4 **Relatedness of Adverse Event to Investigational Protocol**

1. Not Related:	Concomitant illness, accident, or event with no reasonable association with protocol.
2. Unlikely:	The reaction has little or no temporal sequence from administration of the investigational protocol, and/or a more likely alternative etiology exists.
3. Possibly Related:	The reaction follows a reasonably temporal sequence from administration of the investigational protocol and follows a known response pattern to the suspected investigational protocol; the reaction could have been produced by the investigational protocol or could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.
4. Probably Related:	The reaction follows a reasonably temporal sequence from administration of investigational protocol; is confirmed by discontinuation of the investigational protocol or by re-challenge; and cannot be reasonably explained by the known characteristics of the subject's clinical state.
5. Definitely Related:	The reaction follows a reasonable temporal sequence from administration of investigational protocol; that follows a known or expected response pattern to the investigational protocol; and that is confirmed by improvement on stopping of the investigational protocol, and reappearance of the reaction on repeated exposure.

9.3.5 **Recording of Adverse Events**

All clinical adverse events are recorded in the Adverse Event (AE) Log in the subject's study binder. Study staff should fill out the AE Log and enter the AE information into the EDC system within 48 hours of learning of a new AE or receiving an update on an existing AE.

Entries on the AE Log (and into the EDC) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

9.3.6 **Adverse Events and Serious Adverse Events - Reportable Events**

The following are considered reportable events and must be reported via the EDC system within 24 hours of study staff being notified of the event.

- All events that meet the above criteria for Serious Adverse Events

9.4 **Safety and Feasibility of Performing Virtual Experimental Visits**

The study will be performed virtually via videoconferencing. Before each visit, the subject will be asked to provide their physical location. If an emergency does occur while the videoconference is underway, 911 will be called promptly. The research team will follow up with the subject as soon as it is safe and appropriate to do so.

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