Impact of Photobiomodulation (PBM) on Biomarkers of Alzheimer's Disease

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STATEMENT OF COMPLIANCE

*Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an **intramural** NIH study, use the second statement below:*

(1) [The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.]

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 08 April, 2022

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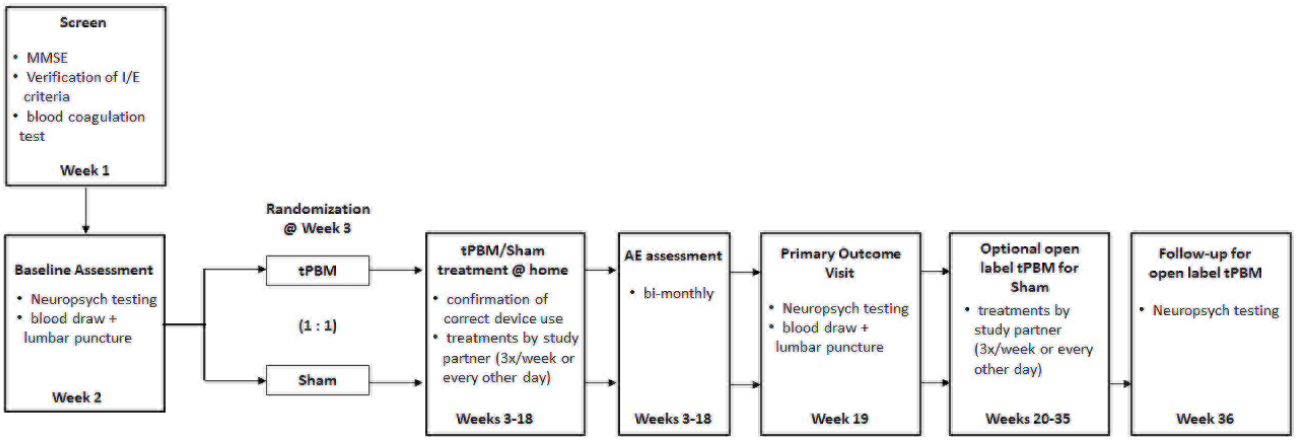
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Examining the Impact of Photobiomodulation on Cognition, Behavior, and Biomarkers of Alzheimer's Disease.
Study Description:	The proposed sham-controlled pilot trial will investigate the safety and tolerability of 16 weeks of home transcranial photobiomodulation (tPBM) treatment with commercially available device (i.e., Vielight Neuro Gamma) in 14 patients with mild-to-moderate Alzheimer's Disease (AD). We will also examine the effects of home PBM on the cognitive function, behavioral symptoms, cerebrospinal fluid and blood biomarkers of AD pathology, including amyloid burden, tangle pathology, axonal injury, microglia activation/inflammation, and neurotrophic factors. We hypothesize that home PBM treatments will be safe and tolerable. We further hypothesize that effect sizes will suggest AD patients randomized to the active PBM condition have improved cognitive function and fewer behavioral symptoms after 16 weeks compared to patients randomized to Sham. Based on reports that PBM upregulates neuroprotective factors, reduces neuroinflammation, induces peripheral and central nerve regeneration, and prevents degeneration, we hypothesize that these behavioral improvements will correlate with changes in fluid biomarkers of neurodegeneration (i.e., neurofilament light chain, NfL) and Alzheimer's disease (e.g., Aβ42 and Aβ42/Aβ40, total- and phosphorylated-tau).
Objectives:	Primary Objective: Examine the safety and tolerability of home tPBM delivered with a commercially available PBM device. Secondary Objectives: Examine the effects of home tPBM on cognition, behavior, and fluid biomarkers of AD.
Endpoints:	Primary: All adverse events Secondary: Change in ADAS-cog and biochemical biomarkers (Aβ40, Aβ42, total and phosphorylated tau, NfL)
Study Population:	Men and women, ages 50 years or older with have prodromal, mild or moderate typical or atypical AD, supported by clinical AD biomarkers and a Mini-Metal State Exam (MMSE) score > 13.
Phase or Stage:	1B
Description of Sites/Facilities Enrolling Participants:	San Francisco VA Medical Center and University of California Memory and Aging Center
Description of Study Intervention/Experimental Manipulation:	Transcranial and intranasal photobiomodulation, delivers near-infrared light (λ = 810 nm, 40 Hz, 40-150 mW/cm^2) to the scalp and one nostril.
Study Duration:	36 months
Participant Duration:	4-8 months

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

	Screening (Week 1)	Baseline (Week 2)	Sham/real Treatments (wks 3-18)	Primary Outcome (week 19)	Optional Open label tPBM (wks 20-35)	Follow-up for open label tPBM (week 36)
Informed Consent	X					
MMSE	X					
Blood coagulation test	X			X		
Demographics	X					
Inclusion/exclusion	X					
Outcome Evaluation						
ADAS-cog, CCT, NPI, ADCS-ADL		X		X		X
Blood draw + LP		X		X		
Randomization		X				
Control & Experimental Interventions		X	X		X	X
Adverse Events Reporting		X	X	X	X	X

2 INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder defined by the concomitant brain accumulation of extracellular amyloid $\beta_{1\text{-}42}$ (Aβ) plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated forms of the 3/4-repeat microtubule associated protein tau (Jack et al., 2018). The pathophysiology of AD includes early significant brain metabolic and bioenergetic changes. These have been disputed to be secondary to atrophy and neurodegeneration, but evidence suggests that Aβ and tau accumulation are indeed preceded by a cascading network failure that affects the default mode network (DMN), the most vulnerable functional network in AD (Jones et al., 2016). In asymptomatic carriers of AD-causing mutations, early detectable changes include hyperactivation of memory networks, as detected by brain functional magnetic resonance imaging (fMRI) (Fuller et al., 2019). Asymptomatic autosomal AD-mutation carriers eventually display DMN hypometabolism, compared to age-matched carriers that exceeds tissue loss (Mosconi et al., 2008). This supports that energy metabolism changes may be key in a neurodegeneration spiral that involves energy failure, alteration of housekeeping mechanisms, proteinopathy and cell death. Targeting neurometabolic changes may have therapeutic potential in AD.

Photobiomodulation with infra-red low-level therapy is an emerging neuroprotective and cognitive-enhancing intervention with potential therapeutic value in AD. In pre-clinical models, photobiomodulation exerts neuroprotective effects by stimulating cytochrome *c* oxidase (CO), a key enzyme in the mitochondrial respiratory chain (Karu, 1989; Rojas and Gonzalez-Lima, 2011; Salehpour et al., 2018). CO is the rate limiting step in the synthesis of adenosine triphosphate and regulates converging bioenergetic, oxidative stress and cell-death pathways (Wong-Riley, 1989; Rojas and Gonzalez-Lima, 2011; Wong-Riley, 2012). Photobiomodulation impacts energy formation and oxidate stress (ON effects), and a number of downstream intracellular mechanisms regulating synaptic function, calcium homeostasis and cell survival signaling (OFF effects) (Karu, 1988; Rojas and Gonzalez-Lima, 2016).

In animal models, transcranial photobiomodulation (tPBM) increases *in situ* brain oxygen consumption and brain metabolic capacity (Rojas et al., 2012), increases expression of brain anti-oxidant enzymes (Rojas et al., 2008; Meynaghizadeh-Zargar et al., 2020), prevents neurodegeneration induced by mitochondrial toxins (Eells et al., 2003; Rojas et al., 2008; San Miguel et al., 2019) and enhances learning and memory (Rojas et al., 2012; Gutierrez-Menendez et al., 2021; Hosseini et al., 2021; O'Donnell et al., 2021). In humans, tPBM increases regional cerebral blood flow (Wang et al., 2017; Saucedo et al., 2021), executive function (Barrett and Gonzalez-Lima, 2013; Vargas et al., 2017), increases electrophysiological resting state signals (Vargas et al., 2017; Spera et al., 2021) and enhances functional connectivity, measured with functional magnetic resonance imaging (fMRI) (Dmochowski et al., 2020). In individual with cognitive impairment, tPBM improves cognitive function (Berman et al., 2017; Nizamutdinov et al., 2021) and DMN brain functional connectivity (Chao, 2019). The clinical and neurochemical effects of tPBM in individuals with evidence of the AD pathophysiological process have not been previously assessed. The feasibility of a regimented tPBM treatment protocol in people with biomarker-confirmed AD dementia is unknown. The effects of tPBM on plasma and cerebrospinal fluid (CSF) biomarkers in individuals with biomarker-confirmed AD have not been previously investigated.

2.1 STUDY RATIONALE

Among older adults, Alzheimer's disease (AD) is the most common form of dementia, a condition characterized by the loss of higher brain function such as memory, problem-solving abilities, and language. Photobiomodulation (PBM) with transcranial low-level light is a novel, non-invasive intervention that can help regulate brain function. The pathological hallmarks of AD include senile plaques rich in β-amyloid (Aβ) peptide and neurofibrillary tangles composed of hyperphosphorylated tau (p-tau) (Blennow et al., 2006). In animal models of AD, PBM reduces the size and number of brain Aβ plaques (De Taboada et al., 2011; Purushothuman et al., 2014) p-tau, and neurofibrillary tangles (Purushothuman et al., 2014). PBM also mitigates behavioral deficits in transgenic AD mouse models (De Taboada et al., 2011) and humans with dementia (Saltmarche et al., 2017; Berman et al., 2017).

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

General: As in any study, there is a risk of a breach in confidentiality. Violation of confidentiality regarding psychiatric condition may cause problems such as difficulty with employment or insurance coverage or personal embarrassment. Standard precautions will be taken to protect the confidentiality of all research participants, including coding all data and only entering codes (study I.D. numbers, initials and age) in computerized databases. All paper records are kept in locked files in the investigators' offices with access limited to research staff. Only aggregate results are published. All study staff have been trained to current standards and certified in HIPAA regulations; they will carefully apply these standards to their work on this study. All new personnel will complete Good Clinical Practices and HIPAA training prior to beginning work on this study.

Delay in Treatment: By participating in this study, subjects are likely to experience a delay in the initiation of treatment due to evaluation procedures during the Screening Period. Furthermore, since it is unknown whether adjuvant tPBM is effective, study participation could delay potentially effective therapy. During this period, it is possible that the participant's condition could worsen and lead to increased disturbances in mood, sleep, appetite, and cognition. This could result in work loss, loss of social function, and possibly increased risk of suicide. However, the risk should be minimized as there are several safety precautions in place and participants will have frequent contact with study clinicians. In addition, the alternatives to this research are clearly explained to all patients, and treatment strategies that are generally used for patients are discussed. We also inform patients that tPBM is not FDA approved for MCI or dementia.

Stigma: Participation in a "memory and AD study": There is potential negative impact on employment, insurability, or other factors for any subject participating in research studies of "memory and AD".

Medical History: The main risk is a loss of privacy and every precaution is taken to ensure confidentiality. Participants may also experience discomfort or distress when responding to potentially sensitive questions regarding mental illness and drug use.

Psychometric Testing: There are no risks associated with cognitive testing. Some individuals may experience fatigue or test performance anxiety. Periodic breaks will be available during cognitive testing.
Blood draw: Phlebotomy may cause pain, bruising, fainting, or a small infection at the puncture site. In addition, there is a risk of hematoma (a small amount of bleeding into the arm). For the purpose of this

study we will be drawing (approximately 34 mL) total for blood coagulation tests (prothrombin time, partial thromboplatin time, platelet count) prior to the baseline and post-treatment lumbar puncture and for fluid biomarker assessment.

Lumbar puncture (LP): The LP may be associated with pain during the performance of the procedure. This is usually temporary and confined to the lower back. A headache may occur in about 5% of elderly people who undergo lumbar puncture. Less commonly, in about 1-4% of subjects, a persistent low-pressure headache may develop, probably due to leakage of CSF. Lower rates of a post-Lp headache have been noted in elderly patients, and when atraumatic (Sprotte) needles are used. If a post-LP headache persists it may need additional treatment (e.g., with fluids and analgesics). Uncommonly a blood patch (injection of some of the subject's blood to patch the CSF leak) may be needed. Potential but rare risks of lumbar puncture include infection, damage to nerves in the back, bleeding into the CSF space, and death. The risk of these is much less than 1%.

Randomization risks: Subjects will be assigned to a study treatment group by chance, and the study group treatment that subjects receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.

Placebo risks: If subject is in the group that receives Sham PBM treatments, their condition will go without the active (study) PBM treatment for 16 weeks.

Risks for Caregivers/Study Partners: Caregivers/study partners may find it psychologically stressful to answer questions about the patients' behavior. They may also find it stressful to be responsible for the Vielight Neuro Gamma device.

tPBM risks: The safety of one session of tPBM was evaluated in three large RCTs with a pooled sample of 1,410 subjects with stroke (Lampl et al., 2007; Huisa et al., 2013; Zivin et al., 2014). No significant difference in the rate of adverse effects were observed between the group receiving laser NIR (808 nm; 5W) or sham. Two open studies using 1 and 6 sessions of tPBM reported no treatment-emergent side-effects (Hacke et al., 2014; Lampl et al., 2007). A clinical trial with 16 sessions reported an increased number of mild side-effects in the active treatment group, the most frequent being insomnia, "seeing vivid colors", "an ashtray-like taste", and irritable mood (Hipskind et al., 2019). Other potential risks relate to inappropriate administration and will be mitigated by the safety procedures such as the use of protective eye wear. The risk of thermal injury from PBM delivered with the parameters used in the studies we reviewed is considered minimal and limited to the skin. In ten individuals treated for TBI with 10-15W lasers –a much higher power than what is used in tPBM– the skin temperature increased to no more than 30°C with rapid cooling after removal of the NIR light. Clinically, patients reported slight skin warming, but no discomfort (Hipskind et al., 2019). Inherent to the use of any laser device is the potential risk of retinal lesions resulting from improper use of the laser and from the shedding of the light beams straight through lens and from their convergence on the macula; this is mitigated with appropriate safety eyewear and procedures.

There have been no documented risks associated with the Vielight Neuro Gamma device. The Vielight Neuro Gamma device is a portable, wearable, low-light level therapy delivery device that administers near-infrared light to the brain transcranially and intranasally. The device can be applied by the study partner at home and does not require specialized training. The controller houses a NiMH battery and controlling electronics for the Neuro Rx Gamma device. Both the Headset and Nasal Applicator are connected to the controller with connectors that prevent them from being incorrectly inserted. A single

button initiates a software controlled 20-minute therapy – automatically timed but can be discontinued by pressing the button a second time. A single indicator LED flashes at 40 Hz (visible by an observer) when therapy is being delivered and indicates when the device is being charged via its medical grade power supply. The circuitry in the controller manages the other LEDs, delivering NIR light at 810 nm and pulsing at 40 Hz. The headset is an adjustable wearable applicator consisting of a posterior band and anterior band of LEDs. The posterior band contains three LEDs and is intended to be placed over the precuneus, and left and right angular gyri. The anterior band contains a fourth LED is placed centrally on a second anterior band to target the medial prefrontal cortex. The three posterior band LEDs deliver NIR light at 810nm. 100mW of power is provided to each LED at 40 Hz, 50% duty-cycle with a beam spot size of 1cm.2 The anterior band LED delivers infrared light at 810nm. 75mW of power is provided to the LED at 40 Hz, 50% duty-cycle with a beam spot size of 1cm2. The nasal applicator consists of a single LED that is placed in the nostril and clipped into place. The nasal LED has an 810nm wavelength and has an output power of 25mW delivered to a beam spot size of 1cm2. A medical grade, certified DC supply is used to power the device and charge the three NiMH internal batteries. Once the headset and nasal applicator have been positioned, the operator of the device (i.e., study partner) initiates the procedure by pressing a single button on the controller. The device proceeds to deliver light to each LED at 40 Hz 50% duty cycle for 20 minutes and stops automatically. During the 20-minute treatment, the indicator LED on the controller flashes at 40 Hz. The operator is notified that the procedure is finished when the indicator LED on the controller stops flashing and the device beeps 3 times.

The risks to the patient and operator are no greater than for other LED-based therapies that are intended for use without clinical supervision. The device is intended as an adjunct to current pharmacological therapies and is not intended to replace those therapies; therefore, lack of efficacy does not pose a significant risk in the context of this clinical trial. During the clinical trial, patients will be proactively assessed for adverse effects on an ongoing basis. The risks associated with the use of the Vielight Neuro Gamma device are equivalent to those for other low-level light therapy class II devices.

There were no significant or any adverse events in the PI's other study involving the Vielight Neuro Gamma device (Chao, 2019). However, one study partner, who do not have dementia, reported feeling "tired" after he tried using the Vielight Gamma device for 20 minutes. There were also no significant or any adverse events reported in the Saltmarche et al. (2017) study, which used the similar Vielight Neuro Alpha device in elderly patients with dementia

2.2.2 KNOWN POTENTIAL BENEFITS

The potential direct benefit of tPBM treatment is that the subjects may experience an improvement in cognitive and behavioral symptoms. The study team (in addition to the study consent) will clearly inform participants that the study does not provide clinical treatment and should not be used as a substitute for proper medical care with a physician; however, if the standard medical, neurological, or psychiatric evaluations reveals significant deficits or an emergent and previously undiagnosed medical condition, or if the blood assays reveal significant abnormalities, this information will be discussed with the participant and transmitted to their primary care physician (PCP).

The indirect benefits to subjects are more considerable, however, as we believe that this study will greatly increase our understanding of the potential roles of tPBM in AD. If this project is successful, it will inform decisions about whether the tPBM has the potential to substantially reduce cognitive and behavioral symptoms associated with AD. Society will benefit from advances in the understanding of AD and diagnostic strategies proposed by these studies.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

PBM therapy may be less effective or have more side effects than other available therapies/treatments for dementia. This will not be known until after the study is completed and the data have been analyzed. There also may be risks that are unforeseeable. We will minimize other risks associated with the study:

Minimalizing risks associated with obtaining medical history: Questioning regarding psychiatric disorders or symptoms and substance abuse will be limited to a format that is typical for a routine medical history.

Minimizing risk of psychological or emotional distress related to research assessments: Research staff who administer baseline and follow-up assessments will be carefully trained using standard procedures on strategies for working with individuals with dementia and their caregivers in a sensitive and respectful manner. Participants and caregivers will not be forced to answer any questions. Staff will be trained to recognize and appropriately address signs of discomfort or stress when indicated (e.g., by taking breaks, rescheduling appointment, skipping sections that cause undue discomfort).

Minimalizing risks associated with LPs: The LPs will be performed by neurologists who are specifically trained in the procedure. As previously described the lumbar puncture needle has been selected based on evidence-based practice findings for the prevention of side effects.

Minimizing risks associated with blood draws: Blood draws will be performed by a trained nurse or phlebotomist at the UCSF Memory and Aging Center.

Minimizing risk of loss of privacy: We will minimize risk of loss of privacy by training all research staff to maintain data in a secure manner and not to discuss study participants outside the research team. Research data will be stored in locked file cabinets or on VA-approved devices (e.g., VA-encrypted laptops) or secure VA servers. Study forms will include unique ID numbers but not names or other identifying information whenever possible.

The research is justified because the risks to subjects is very low and the knowledge that could be gained from the study may aid with development and implementation of therapies that enhance brain function and quality of life in individuals with Alzheimer's disease.

3 OBJECTIVES AND ENDPOINTS

The primary objective of the study is to assess the safety and tolerability of home transcranial photobiomodulation (tPBM) treatments delivered with a commercially available PBM device (i.e., the Vielight Neuro Gamma device). The primary endpoint will be all adverse events.

The secondary objects of the study are to examine the effects of home tPBM on cognition, behavior, and fluid biomarkers of AD in patients with biomarker confirmed diagnoses of mild-to-moderate AD. Secondary endpoints will be change in the Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-cog), and change in fluid biomarkers of AD (e.g., Aβ40, Aβ42, total and phosphorylated tau, neurofilament light chain).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study will evaluate the safety and tolerability of home transcranial photobiomodulation (tPBM) treatments for patients with mild-to-moderately severe Alzheimer's Disease (AD, ages 50 and older) in a phase Ib, parallel design, sham-controlled, randomized clinical trial lasting 16 weeks. At baseline, all subjects will complete initial neuropsychological testing. To elucidate mechanisms of action of tPBM, prior to treatment, subjects will undergo blood draw and lumbar puncture to ascertain baseline levels of AD-related biomarkers. Subjects will then be randomized to tPBM/sham and will undergo 16 weeks of home tPBM treatments, delivered by a study partner/caregiver, 20 min per day, 3 days per week, for 16 weeks. tPBM parameters will be LED clusters placed over the forehead and 3 other scalp sites and intranasally, 810 nm wavelength, and pulse wave.

5 STUDY POPULATION

The study population will include men and women, ages 50 years or older, with have prodromal, mild or moderate typical or atypical AD, supported by clinical AD biomarkers and a Mini-Metal State Exam (MMSE) score > 13.

5.1 INCLUSION CRITERIA

To be eligible to participate in the study, an individual must meet all of the following criteria:

1. Be 50 years or older
2. Have a diagnosis of prodromal or mild-to-moderate AD supported by AD biomarkers (e.g., CSF, amyloid PET or plasma biomarkers)
3. Have a MMSE score between 14 and 30
4. Be fluent in English
5. Have a reliable study partner who will agree to accompany the subject to study visits and spend the necessary time to learn how to use, control, and maintain the Vielight Neuro Gamma device, how to administer tPBM treatments, and how to log its use during the 16 weeks of the study
6. Agree to under two lumbar punctures, approximately 16 weeks apart.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Has a diagnosis of no-AD dementia
2. Has a history of mental retardation or pervasive developmental disorder
3. Has a history of brain parenchymal lesion or epilepsy
4. Has a history of structural brain lesions or stroke temporally related to the onset or worsening of cognitive impairment
5. Has a current diagnosis of alcohol or substance abuse/dependence
6. Has photosensitive reactions to sunlight or visible light (polymorphous light eruption, solar urticaria, persistent light reactivity) or requires photosensitizing medication
7. Has increased skin sensitivity at the treatment site, including active herpes simplex in the treatment area, history of keloid formation, or history of retionid use in the past month
8. Has a prior history of epistaxis
9. Is currently undergoing light therapy

10. Is currently participating in another interventional clinical trial

We will not exclude patients who are currently on a stable dose medication(s) as long as they have been taking the medication for the last 3 months prior to the baseline assessment and do not have plans to discontinue the medication during the 16-week intervention period.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The Vielight Neuro Gamma device, manufactured by Vielight, Inc. (Toronto, Canada) will be used in the study. The parameters of the non-invasive, non-thermal, non-laser PBM device are summarized in Table 1. Although the Vielight Neuro Gamma device is not presently labeled for treating dementia or AD, it is considered a non-regulated, "low risk general wellness product" according to the Food and Drug Administration.

Table 1. Parameters of the Vielight Neuro Gamma Device

Source	light emitting diode (LED)
Wavelength, nm	810
Power output, mW	100 (posterior transcranial LEDs); 75 (anterior transcranial LED); 25 (intranasal LED)
Power density per LED, mW/cm^2	100 (posterior transcranial LEDs); 75 (anterior transcranial LED); 25 (intranasal LED)
Pulse frequency, Hz	40
Pulse duty cycle, percentage	50
Duration of each treatment session, minutes	20
Frequency of treatment	3x/week
Beam spot size, cm^2	≈1
Energy delivered, Joules	225 (transcranial headset); 15 (intranasal LED)
Energy density per LED, J/cm^2	225 (transcranial headset); 15 (intranasal LED)
Dose of each treatment session, Joules	240
Cumulative energy density per LED, per week	675 (transcranial headset); 45 (intranasal LED)
Cumulative dose per week, Joules	720

6.1.2 ADMINISTRATION AND/OR DOSING

The Vielight Neuro Gamma device has light emitting diodes mounted on a headset that targets key nodes of the default mode network (DMN), including one frontal array, two parietal arrays, one posterior array that targets the precuneus and posterior cingulate cortex, and one intranasal probe that targets the mesial temporal lobe. The device delivers infra-red light transcranially at λ = 810, nm, 40 Hz, 40-150 mW/cm^2. These dosimetry parameters achieve 0.9 - 11% transmittance through soft tissue and human skull (Salehpour et al., 2018). tPBM will be administered every other day (or at least 3 times a week) in 20-min fractions for 16 weeks. Patients and study companions will be instructed on the use of the device at rest

(e.g., before going to bed), every other day or 3 times a week (e.g., Monday, Wednesday, and Friday). The sham group will be given the same instructions for use and used the same device, except that the device was blindly set to power output of 0 mW/cm^2. Because the device uses light emitting diodes, it does not produce heat or noise, and the 810 nm wavelength produces non-visible energy. These features were relied on to maintained participants blinded to group allocation.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Study partners will be trained how to position the Vielight Neuro device on the patient, how to administer the tPBM treatments, how to control, clean and maintain Vielight Neuro device in a single session. One week after the training session, the study partners will be asked to demonstrate their ability to correctly position the device and to administer tPBM treatments to the patients. Any mistakes will be corrected, and study partners will be re-trained if necessary. The study partners will be asked to log the tPBM treatments throughout the 16-weeks in a home treatment diary. A study staff will contact the patient and study partner twice a month to assess for adverse events.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Subjects will be randomized 1:1 to either tPBM or sham. Study co-investigator (Dr. Margaret Chesney) will provide the randomization list to study staff as eligible participants are enrolled. Blinding will be maintained because the Vielight Neuro Gamma devices use light emitting diodes, and it does not produce heat or noise, and the 810 nm wavelength produces non-visible energy.

Dr. Chesney will give study staff sealed envelopes with the codes for participant randomizations. The envelopes would be opened only in a situation where an SAE is determined as possibly or potentially related to study intervention. The breaking of the blind will be reported to the IRB, as part of the SAE report.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Subjects may be withdrawn from the study for any of the following reasons:

1. Subject's or Caregiver's choice to withdraw their consent to participate. Any participant has the right to withdraw from the study at any time and for any reasons without prejudice to future medical care by the physician or the institution. This will be considered a screening failure if they withdraw from the study prior to being randomized. Participants who withdraw consent after randomization will have any available data evaluated, up to the time of withdrawal.
2. Investigator's choice to withdraw the subject from the study. This will be considered a screening failure if the Investigator withdraws the patient prior to randomization.
3. Study termination for either administrative or safety reasons.

For participants who are noncompliant with follow up visits, every effort will be made to collect the data requested by this protocol through the follow up period. All data collected up until the period the subject has withdrawn from the study will be used for this study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Cognitive and Behavioral Outcome Measures will be assessed at baseline and after 16 weeks by a study staff member who will be blind to treatment assignment. The measures are standard in the field and have well-established validity and reliability:

- The **Mini-Mental State Exam (MMSE)** (Folstein et al., 1975) is a fully structured screening instrument frequently used for Alzheimer's disease drug studies. The scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons.
- The **Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-cog)** (Rosen et al., 1984) is a structured scale that evaluates memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, and ability to remember test instructions are also obtained. The test is scored in terms of errors, with higher scores reflecting poorer performance. Scores can range from 0 (best) to 70 (worse).
- The **Color Trails Test (CTT)** (D'Elia et al., 1996) is a non-verbal test of visual attention, graphomotor sequencing, and effortful executive processing abilities (i.e., sustained attention and set shifting).
- The **Neuropsychiatry Inventory (NPI)** (Cummings, 1997) is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with a study companion or qualified partner.
- The **Alzheimer's Disease Cooperative Study, Activities of Daily Living (ADCS-ADL)** (Galasko et al., 1997) assesses the competence of patients with AD in basic and instrumental activities of daily living (ADLs). It can be completed by a caregiver in questionnaire format, or administered by a clinician/researcher as a structured interview with a caregiver.

Cerebrospinal fluid (CSF) and blood biomarkers: The Quanterix HD-1 analyzer will be used for automated multiplex quantification of proteins in biofluids, including plasma, serum and CSF. The HD-1 platform uses Single Molecule Array (SiMoA) technology, a digital form of ELISA with a 1000-fold higher sensitivity compared to other immunoassay techniques. This methodology offers high precision (coefficient of variations below 10%), efficiency (2.5 hours per 96-well plate), wide dynamic range (spanning > 4 logs) and capabilities for homebrew assay development. Ten mL of blood sample will be collected from each patient by venipuncture red-top or ethylenediaminetetraacetic acid (EDTA) tubes for serum and plasma. Ten mL of CSF will be collected by LP into polypropylene tubes according to the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (*http://www.adni info.org/ADNIStudyProcedures/LumbarPunctures.aspx*). $A\beta_{1–40}$, $A\beta_{1–42}$, total tau, NfL, UCHL1, MCP-1, MCP-3, MIP-1β, VEGF, and BDNF will be measured from blood. These analytes and p-tau will be measured from CSF.

8.2 SAFETY ASSESSMENTS

Study staff will call the subject and his/her study partner twice a month to for safety assessments.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

An ***adverse event*** (AE) is any symptom, sign, illness, or experience that develops or worsens in severity during the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Severity will be determined from the grades presented in National Cancer Institute (USA) Common Terminology Criteria for Adverse Effects version 4.0 (published August 9, 2006) (CTCAE v4.0) guidelines. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 – Mild AE
Grade 2 – Moderate AE
Grade 3 – Severe AE
Grade 4 – Life-threatening or disabling AE
Grade 5 – Death related to AE

All adverse events will be monitored until they are adequately resolved or explained

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Each adverse event will be judged by the Investigator as to its relationship and level of relatedness to the investigational device. Relatedness will be scored consistent with CTCAE v4.0 guidelines:

Unrelated – the AE is clearly not related to the investigational agent(s),
Unlikely – the AE is doubtfully related to the investigational agent(s),
Possible – the AE may be related to the investigational agent(s),
Probable – the AE is likely related to the investigational agent(s),
Definite – the AE is clearly related to the investigational agent(s).

8.3.3.3 EXPECTEDNESS

The principal investigators will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in this protocol for the study agent.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or during the bi-monthly check-ins. All AEs including local and systemic reactions not meeting the criteria for SAEs will be logged. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unexpected problems (UPs) will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, and at the bi-monthly check-ins, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.3.5 ADVERSE EVENT REPORTING

AEs that are unanticipated, determined to be at least "probably related" to the study intervention, and reveal a "greater risk of harm" than originally expected will be considered reportable new information and reported within 5 business days of the principle investigator(s) becoming aware of the event.

Reports, signed by a principle investigator, will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome is unanticipated, at least probably related to the study intervention, and reveals a "greater risk of harm" than originally expected;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated adverse events.

All other adverse events will be reported annually to the IRB.

Note that the period of trial participation is defined as occurring between randomization and close of the last visit window as defined by the protocol. Therefore, only AEs occurring after randomization and before the close of the last visit window will be logged. UPs that are not AEs will be noted separately between time of trial enrollment and study completion.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be reported to the IRB as soon as possible and certainly within 5 business days of the principle investigator(s) becoming aware of the event.
Reports, signed by a principle investigator, will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a serious adverse event;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the serious adverse event.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e., not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e., possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)

• Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Unanticipated problems that are determined to be at least "probably related" to the study intervention, and reveal a "greater risk of harm" than originally expected will be considered reportable new information and reported within 5 business days of the principle investigator(s) becoming aware of problem. Other unanticipated problems will be reported within 10 business days of the principle investigator(s) becoming aware of the problem.

Reports, signed by a principle investigator, will include the following information:

• Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
• A detailed description of the event, incident, experience, or outcome;
• An explanation of the basis for determining that the event, incident, experience, or outcome is unanticipated, at least probably related to the study intervention, and reveals a "greater risk of harm" than originally expected;
• A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint:

We hypothesize home transcranial photobiomodulation (tPBM) treatments delivered with the NeuroGamma device will be safe and that patients with mild-to-moderate AD will find home tPBM treatments tolerable.

- Secondary Endpoint(s):

We hypothesize that AD patients randomized to active tPBM have improved cognitive function (i.e., performance on the ADAS-cog, and CTT) and behavioral symptoms (i.e., NPI and ADCS-ADL) after 16 weeks compared to patients in the Sham group.

We hypothesize that AD patients randomized to active tPBM have decreased levels of NfL after 16 weeks compared to patients in the Sham group.

In exploratory analyses, we will examine the effects of 16 weeks of PBM on fluid levels of Aβ42 and Aβ42/Aβ40, total- and p-tau. We will also explore the relationship between chances in cognition and behavior with changes in fluid biomarkers.

9.2 SAMPLE SIZE DETERMINATION

The purpose of the proposed study is to gather the data required so that effect size estimates may be calculated for each of the study hypotheses. Moreover, there are no published human studies on the effects of tPBM on levels of these biomarkers. Therefore, one of the goals of this study is to obtain a reliable effect size estimate of tPBM on brain function and fluid biomarkers of neurodegeneration, inflammation, and neurotropic factors in anticipation of a larger PBM dementia trial. Power analyses suggest that based on our proposed sample size (8 randomly assigned to tPBM and 8 to sham), at power =.80 and alpha=.05, we will be able to detect evidence of meaningful between-group differences (≥0.25 SDs) in the behavioral and biomarker outcome measures.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

Categorical and continuous demographic and clinical data will be compared between groups with the Fisher's exact or non-parametric Kolmogorov-Smirnov tests. Biomarker data will be inspected for normality with the Shapiro-Wilk test. Associations between clinical and biomarker data will be analyzed with Spearman correlations. Given the exploratory nature of the study, correlations will not be corrected for multiple comparisons and only uncorrected results are presented. Changes in clinical variables and biomarkers will be determined by calculating a change score as the ratio of value at week 16 over the value at baseline. Thus, a change score of 1 will signify no change compared to baseline and change scores < 1 and > 1 reflect, respectively, a decrease or an increase in the neurocognitive or functional scale score or biomarker concentration at week 16, compared to baseline. Between-group change scores will be compared with the non-parametric Kolmogorov-Smirnov tests.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Safety and AEs will be assessed at each in-person study visit and during bi-monthly check-ins. We will use Kolmogorov-Smirnov test to compare the number of AEs in each group. To examine tolerability, we will determine the total number of treatment days and average treatment days per week in each group.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Kolmogorov-Smirnov tests will be used to compare clinical and biomarker change scores in the two groups. Associations between clinical and biomarker data will be analyzed with Spearman correlations.

9.3.4 BASELINE DESCRIPTIVE STATISTICS

Categorical and continuous demographic and baseline clinical data will be compared between groups with the Fisher's exact or non-parametric Kolmogorov-Smirnov tests.

9.3.5 PLANNED INTERIM ANALYSES

N/A

9.3.6 EXPLORATORY ANALYSES

In exploratory analyses, we will examine the effects of 16 weeks of PBM on fluid levels of Aβ42 and Aβ42/Aβ40, total- and p-tau. We will also explore the relationship between chances in cognition and behavior with changes in fluid biomarkers.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks will be given to the participant and his/her study partner. Written documentation of informed consent will be required prior to starting intervention/administering study product.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Written consent will be obtained by one of the PIs and/or study staff at the screening visit prior to any study procedures. Due to the complexity of neurodegenerative disease trials and the population being studied, our process is that we will send a copy of the informed consent form (ICF) to potential subjects and caregivers (signature line crossed through) in advance of the first study visit where written informed consent occurs. The purpose is to allow ample time for subjects/families to contemplate study participation and for the PI and study team to answer questions and provide clarification regarding the ICF document and process.

At the in-person consenting visit, before any study procedures occur, a copy of the California Experimental Subject's Bill of Rights is provided and discussed. The ICF is presented and written informed consent is obtained. We routinely schedule a minimum of 1 hour for the consenting process at the first visit to allow discussion and to assure that all questions are answered, and capacity is determined.

A study personnel will explain the purpose, procedures, and potential risks and benefits of the study. The primary study participant (or PP) and his/her legally authorized representative (LAR) will be given opportunities to ask questions. A study personnel will then ask questions of the primary study participant to assess his/her capacity to consent. The assessment form is included for review. If the PP demonstrates capacity to consent, the research staff will politely ask the LAR to leave the room for a few minutes so that the PP can be asked again, separate from his/her LAR whether or not s/he wishes to participate in the study. If the PP answers "yes" and exhibits evidence of understanding what is involved in study

participation, s/he will sign the consent form for him or herself that will be approved by the UCSF and SFVA Institutional Review Boards as indicated. A copy of the signed consent form will be given to the PP and his/her LAR. The PP's capacity to consent will be evaluated using the standards and procedures adapted from the standardized and validated instrument that can be tailored to the specific study protocol, such as the MacArthur Competence Assessment Tool – Clinical Research (MacCAT-CR) developed by Appelbaum and Grisso (1995) as described below and the results will be recorded on a Capacity Assessment Record (CAR). Even when there is an indication of diminished capacity, the presumption of capacity remains. There are four different standards that we use to assess capacity. They are listed below in rough order of ascendancy. We accept a subject as competent to consent to research only when the person is judged capable with regard to all 4 standards.

Standard 1. Did the research candidate "make a choice"? "This standard focuses on the presence or absence of a decision and not on the quality of the decision" This is simply a question as to whether the subject can evidence a choice. If the subject offers a consistent choice about participating in the study this standard is met. If the subject's choice is ambiguous, either because it is inconsistent or unclearly demonstrated, then the standard is failed.

Standard 2. Did the research candidate show "understanding"? "This standard requires memory for words, phrases, ideas, and sequences of information, and also comprehension of the fundamental meaning of information about treatment." A subject need not demonstrate complete or comprehensive understanding of the study in order to meet this standard. However, verbatim recitation of fact without evidence of comprehension is not sufficient either. Consider whether or not the potential subject grasps sufficient information to form the basis for a reasoned decision. If the subject comprehends and remembers (even with assistance) a) that participation is voluntary, b) the major procedures, c) main risks, and d) benefits, then this standard is met. Failure on any element (a-d) means this standard is failed.

Standard 3. Did the research candidate show "reasoning/rational reasons"? This standard tests the capacity to use logical processes to compare the benefits and risks of various treatment options and weigh this information to reach a decision. " The core of this standard is the ability to logically compare risks and benefits in order to reach a rational decision regarding participation. To meet this standard the subject needs to demonstrate the ability to consider both risk and benefit in relation to each other and use the information in a logical manner to come to a decision.

Standard 4. Did the research candidate show an "appreciation" of the personal risks/benefits of the study? "This standard emphasizes the patients' awareness of the consequences of a treatment decision: its emotional impact, rational requirements and future consequences." Appreciation seems to imply something more than an intellectual understanding, and incorporates an affective judgment of the impact of study participation in the context of the particular individual in his or her particular situation. Meeting standard 3 would seem to generally suffice for meeting this standard as long as the subject has a realistic understanding of his or her circumstances.

Assent: If the investigator determines that the PP lacks decision making capacity, the investigator shall inform the PP that his/her LAR is being asked to sign on their behalf, and the PP will be asked to assent to study procedures. This discussion will be documented in the research file. If the PP expresses resistance or dissent to participation or to the use of surrogate consent, the subject shall be excluded from the research study. We will follow the guidelines for surrogate consent established by the University of California-Office of the President and the guidelines in VHA Handbook 1200.05, including section 20 on surrogate consent on research involving persons who lack decision-making capacity.
Assent implies willingness or, minimally, lack of objection to taking part. It does not imply understanding. An interpretable statement from the subject regarding assent must be taken as valid regardless of the subject's level of confusion or dementia. Thus, a statement such as "whatever my wife

says is OK with me" is fine. The demonstration of assent need not be verbal. Passive lack of objection is acceptable in an alert patient. Signs of dissent may include verbal statements as well as non-verbal cues such as shaking their head no or appearing to be agitated or distressed. These signs will be taken as refusals to assent to the study. The LAR may participate as the study partner or may designate another person (e.g., another family member, paid caregiver) to participate as the study partner on their behalf.

Because study partners will also be actively participating in the study (by providing information about the participant's memory, behaviors, and daily functioning), they will also sign a separate consent form. If the LAR is unable to participate in the consent visit in person (e.g., lives remotely), the consent forms may be mailed to them, reviewed with the research team over the phone, signed and mailed back; however, the participant must still provide assent. The study caregiver may also choose to have the consent form mailed to them, reviewed by phone, signed and mailed back. Finally, research staff will sign both forms and will indicate that an assent discussion was completed if appropriate.

The PP will also be provided with a large handout, separate from the consent, that has the PIs' names and phone number so the PP can call the PIs, separate from his/her study partner should s/he wish to do so. In addition, a study staff member will speak to the PP during the Confirmation Visit and during the "check-in" calls, which will occur once every 2 weeks following the Confirmation Visit. On these occasions, the study staff member will speak to the PP separate from the study partner, to see how the study is going for the PP and to ask if the PP still wishes to participate in the study.

There is an 'optional' open-label study phase for eligible participants who complete the placebo-controlled phase and wish to receive active PBM. At the time of initial consent subject may opt in or out of the 'optional' open-label phase by checking boxes on the ICF. We will re-confirm their decision before they start the open-label extension phase.

10.1.2 CONFIDENTIALITY AND PRIVACY

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

Authorized representatives of the sponsor and representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the San Francisco VA Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by San Francisco VA Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the San Francisco VA Medical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Subjects will have the option to allow their leftover blood and CSF samples to be banked indefinitely for future research related to studies on diagnosis of Alzheimer's, disease and/or mechanism of neurodegeneration. Samples will be stored in cryogenic vials with cryogenic printed labels attached to them. The freezers are housed in the UCSF Neurosciences Clinical Research Unit (NCRU).

After the study is completed, the de-identified, archived data will be stored at the NCRU, under the supervision of Dr. Rojas, for use by other researchers including those outside of the study. Permission to store data will be included in the ICF. The NCRU will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant which the PI will have access to as well as study team members he gives permission to on a case-by-case basis. During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. When the study is completed, access to study data and/or samples will be provided through the NCRU. Samples are stored with the study number, subject ID number, and book period number so they can be withdrawn if necessary.

10.1.4 SAFETY OVERSIGHT

Because this is a small pilot study, there will be no Data and Safety Monitoring Board (DSMB) or Safety Monitoring Committee (SMC). Instead, oversight of the trial will be provided by Dr. Julio Rojas (co-PI

and board-certified neurologist), who will be actively involved in the conduct of the study. Dr. Rojas will be responsible for ensuring participants' safety on a daily basis. Drs. Rojas and Chao (co-PIs) will assure that informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data will be accessible at all times for the Drs. Rojas and Chao, to review. The PIs will review accrual, drop-outs, and protocol deviations monthly. Dr. Rojas will review adverse events (AEs) individually real-time and together with Dr. Chao in aggregate monthly. Dr. Rojas will classify each adverse event (AE) for seriousness, severity, expectedness, and potential relatedness to the study intervention, and enter the data into Adverse Event Report Forms. Dr. Rojas will review serious adverse events (SAEs) in real-time. The PIs will ensure all protocol deviations, AEs, and SAEs are reported to the IRB in accordance with the applicable regulatory requirements (i.e., within 24 hours be becoming aware of the SAE). The PIs will also ensure that all information about serious adverse events will be recorded.

10.1.5 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Check (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.6 DATA HANDLING AND RECORD KEEPING

10.1.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical staff under the supervision of the PIs. The investigators will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Source documents will be maintained for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a data capture system that will be password protected.

10.1.6.2 STUDY RECORDS RETENTION

The study records will be considered VA research records and will be retained in accordance with the VHA Records Control Schedule.

10.1.7 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with International Conference on Harmonisation ("ICH") E6:
- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the PIs/study staff to use continuous vigilance to identify and report deviations. All protocol deviations will be addressed in study source documents.

Protocol deviations must be reported to the IRB per their guidelines. The PIs/study staff is responsible for knowing and adhering to IRB requirements.

Protocol deviations must be reported to the local IRB per their guidelines. The PIs/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.8 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.2.

10.1.9 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the San Francisco VA and UCSF has established policies and procedures for all study

group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS AND SPECIAL TERMS

Aβ	Amyloid beta
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale, Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study, Activities of Daily Living
AE	Adverse Event
CAR	Capacity Assessment Record
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CO	Cytochrome c oxidase
CRF	Case Report Form
CSF	Cerebrospinal fluid
CTT	Color Trails Test
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMN	Default Mode Network
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
fMRI	Functional Magnetic Resonance imaging
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
J	Joules
LAR	Legally authorized representative
LED	Light emitting diode
LP	Lumbar puncture

min	minutes
MacCAT-CR	MacAuthur Competence Assessment Tool-Clinical Research
MMSE	Mini-Mental State Exam
MOP	Manual of Procedures
mW	milliwatt
NCRU	Neurosciences Clinical Research Unit
NCT	National Clinical Trial
NfL	Neurofilament light
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
nm	nanometer
NPI	Neuropsychiatric Inventory
OHRP	Office for Human Research Protections
PBM	Photobiomodulation
PCP	Primary Care Physician
PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigator
PP	Primary Participant
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
tPBM	Transcranial Photobiomodulation
UCSF	University of California, San Francisco
UP	Unanticipated Problem
US	United States
VA	Veterans Affairs
VHA	Veterans Health Administration
W	Watt

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