# Modulation effects of a novel body-mind intervention on subjective cognitive decline

**Protocol Number: 06222022**

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**Principal Investigator: Yi-Yuan Tang, Ph.D.**

**Sponsor: Arizona State University**

**Grant Title: Modulation effects of a novel body-mind intervention on subjective cognitive decline**

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**2022-06-22**

***Summary of Changes***

| Version | Date |
|---|---|
| 1.0 | 2022-02-10 |
| 1.1 | 2022-06-22 |

**CONFIDENTIALITY STATEMENT**

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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## STATEMENT OF COMPLIANCE

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: 03-18-2024

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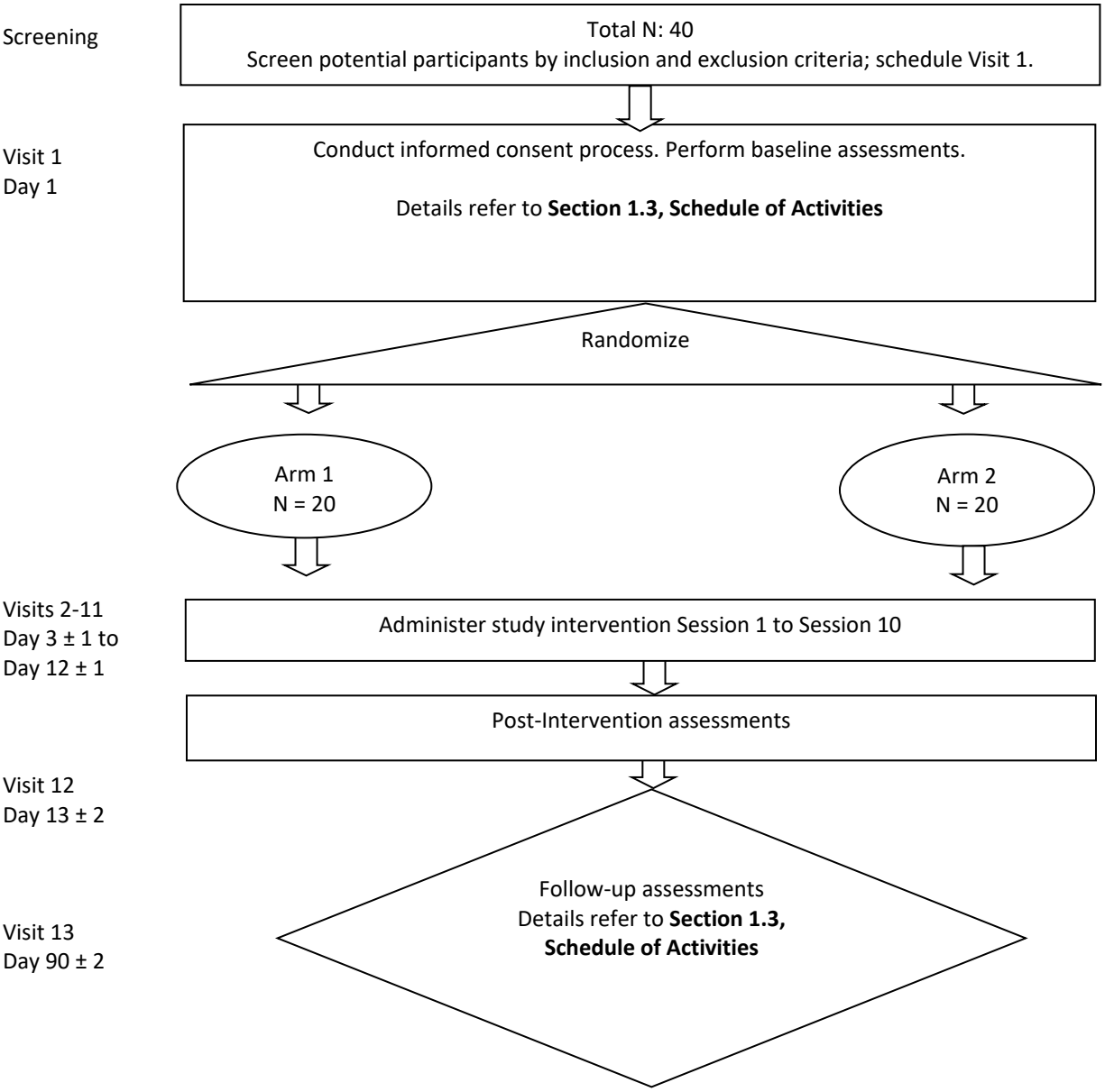
# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **Title:** | Modulation effects of a novel body-mind intervention on subjective cognitive decline |
| **Grant Number:** | *R61AT010138-02S1* |
| **Study Description:** | *The study aims to understand the mechanisms and training effects of evidence-based body-mind training on improving cognitive performance and preventing cognitive decline. Specifically, it aims to investigate the modulation effects of a novel body-mind intervention on subjective cognitive decline (SCD) using an evidence-based preventive intervention - integrative body-mind training (IBMT).* |
| **Objectives:** | *Primary Objective: This study aims to investigate the modulation effects of a novel body-mind intervention on behavioral and cognitive outcomes.*<br>*Secondary Objectives: This study aims to investigate the modulation effects of a novel body-mind intervention on brain outcomes.* |
| **Endpoints:** | *Primary Endpoint: Behavioral and cognitive outcomes*<br>*Secondary Endpoints: Brain outcomes* |
| **Study Population:** | *40 adults (both sexes) between the age 40-65 years old with SCD in the Phoenix, AZ area.* |
| **Phase or Stage:** | *N/A* |
| **Description of Sites/Facilities Enrolling Participants:** | *The participating site/facility is Arizona State University, where enrollment of participants happens. There is no foreign site.* |
| **Description of Study Intervention/Experimental Manipulation:** | *Experimental manipulation is evidence-based preventive intervention - integrative body-mind training (IBMT) and will be offered as a group for 10 sessions.* |
| **Study Duration:** | *12 months* |
| **Participant Duration:** | *3 months* |

## 1.2 SCHEMA

***Figure 1. Flowchart of screening, inclusion, and assessment process***



## 1.3 SCHEDULE OF ACTIVITIES

| | Screening | Visit 1<br>Day 1 | Visit 2 to Visit 11<br>Day 3 ±1 to Day 12±1 | Visit 12<br>Day 13 ±2 | Visit 13<br>Day 90 ±2 |
|---|---|---|---|---|---|
| Review Eligibility | X | | | | |
| Informed Consent | | X | | | |
| Demographics | | X | | | |
| Outcome Evaluation | | | | | |
| Behavioral Assessment (Emotion Regulation Questionnaire; Five Facet Mindfulness Questionnaire; Subject Cognitive Decline Questionnaire) | | X | | X | X |
| Brain Assessment (MRI scan) | | X | | X | X |
| Randomization | | X | | | |
| Control & Experimental Interventions | | X | X | | |
| Adverse Events Reporting | | X | X | X | X |

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

More than five million people in the US have Alzheimer's Disease (AD), at a cost to society of more than $200 billion per year. However, available preventions and treatments have limited efficacy. It is imperative to develop evidence-based programs to help promote cognitive functioning in older adults. We propose to address this urgent and critical public health issue by examining the effectiveness of a brief evidence-based mindfulness intervention – Integrative Body-Mind Training (IBMT) in old adults with SCD through randomized clinical trials (RCTs). We will examine if the intervention can improve behavioral and cognitive functioning, as well as brain changes in these older adults. Outcomes from this study will inform prevention and treatment option to promote health and well-being for individuals with SCD, MCI, and ADRD.

## 2.2 BACKGROUND

Subjective cognitive decline (SCD), the self-reported perception of memory or cognitive problems, is a risk factor for the development of clinical cognitive decline such as MCI and ADRD. Since SCD manifests prior to the onset of clinical impairment, it might provide an optimal stage of time at which to intervene with preventive therapies for ADRD before the progressive neurological loss and irreversible cognitive impairment.[49-52] Recently, few mind-body interventions such as Tai Chi and mindfulness suggested promising effects in preventing cognitive decline. However, these interventions often require longer training time to achieve modest benefits, making them less optimal for old adults to rapidly learn and achieve desirable outcomes.[53-63] Thus, choosing short-term effective interventions in improving targeted outcomes is highly critical for this time-sensitive aging cohort. Moreover, most mindfulness studies on cognitive decline are cross-sectional, which are highly susceptible to confounds and noises. [73-75.] Previous SCD studies showed brain functional and structural abnormalities are associated with clinical progression and annual decline on executive functioning, attention, memory, and global cognition. [66-72.] Self-control and attention deficits can be improved through brief intervention. Our preliminary RCTs in healthy adults provide support for our clinical trial by showing improvement in self-control, attention, cognitive functioning, emotion, stress reduction, and quality of life following brief IBMT intervention, [1-45] suggesting its potential effectiveness in older adults with SCD.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

*The study includes behavioral, cognitive, and brain assessments, as well as mindfulness-based intervention.*

*Behavioral and Cognitive Assessments*

- *Immediate risks: Potential boredom from completing the questionnaires and interviews.*
- *Long-term risks: Data including self-report, questionnaires and interview involve risk of breaches in confidentiality.*
- *Alternative procedures: There are no other available alternative procedures to assess behavior and cognition, since to assess the behavior and cognition, we have to use the actual assessments. To minimize immediate risks, breaks in between questionnaires and interviews are offered to reduce*

*boredom. To minimize long-term risks, all information about the specific individuals will be maintained as confidential. Absolutely no names of subjects are used in published reports or in presentations in scientific meetings. All data will be kept in locked files and digital media in the PI's laboratory. Reference to individual subject data will be made with a number and letter code for each subject. Any risks to participants are minimal and are outweighed by the benefits of increasing our scientific understanding of improving cognitive function in older adults.*

*Brain Assessments*

- *Immediate risks: Potential boredom from completing the MRI scan, the possibility of becoming uncomfortable in the enclosed space of the scanner.*

- *Long-term risks: MRI data involves risk of breaches in confidentiality.*
- *Alternative procedures: There are no other available alternative procedures to brain, since to assess the brain, we have to use the actual MRI assessments.*

*Mindfulness-based Intervention*

- *Immediate risks: Potential boredom from completing the intervention.*

- *Long-term risks: No known risk based on our previous studies [1-12].*
- *Alternative procedures: There are no other available alternative procedures, since the goal is to test the effects of the mindfulness-based intervention. To minimize immediate risks, breaks during the session are offered to reduce boredom.*

### 2.3.2 KNOWN POTENTIAL BENEFITS

*Immediate potential benefits*

*The immediate potential benefits from participant in this study include that participants generally find the experimental paradigms enjoyable (i.e. meditation state) during the intervention sessions [2, 19-21].*

*Long-term potential benefits*

*The long-term potential benefits include that participants have the opportunity to learn more about approaches and methods of improving attention, cognition, emotion and quality of life during the intervention and may be able to apply the learned knowledge in their everyday life.*

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

*Because this is a study that examines the effects of an intervention on behavior, cognition, and behavior, it is inevitable to expose participants to risk of boredom during their assessments and interventions, as these assessments and intervention are necessary for us to evaluate the effects of the intervention.*

*To minimize immediate risks of potential boredom from completing the behavioral and cognitive assessments, brain assessments, and mindfulness-based intervention, breaks during the assessments and interventions are offered to reduce boredom and give participants time to rest. To minimize long-term risks, all information about the specific individuals will be maintained as confidential. Absolutely no names of subjects are used in published reports or in presentations in scientific meetings. All data will be kept in locked files and digital media in the PI's laboratory. Reference to individual subject data will be made with a number and letter code for each subject.*

*Based on the risks of boredom and breach in confidentiality, as well as our approaches to minimize these risks, we conclude that any risks to participants are minimal and are outweighed by the benefits of increasing our scientific understanding of improving cognitive function in older adults, as well as the benefits of potentially having the participants learning ways to improve attention, cognition, emotion and quality of life in their everyday life.*

# 3 OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| Primary | | |
| *This study aims to investigate the modulation effects of a novel body-mind intervention on behavioral and cognitive outcomes.* | *Baseline and post-intervention assessments of behavioral and cognitive outcomes (emotion regulation, mindfulness, SCD).* | *The novel body-mind intervention should lead to improvement in behavioral and cognitive outcomes at post-intervention compared to baseline.* |
| Secondary | | |
| *This study aims to investigate the modulation effects of a novel body-mind intervention on brain outcomes.* | *Baseline and post-intervention assessments of brain outcomes (white matter, grey matter, functional connectivity in AD signature regions.* | *The novel body-mind intervention should lead to improvement in brain outcomes at post-intervention compared to baseline.* |
| Tertiary/Exploratory | | |
| *N/A* | *N/A* | *N/A* |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

*The study is a randomized control trial (RCT) involving two groups – IBMT (Arm 1: experimental manipulation) and health education (HE) (Arm 2: control group) group. Participants in each group will be assessed at baseline, post-intervention, and at 3-month follow-up using behavioral, cognitive, and brain assessments as described in Section 1.3. Automatic randomization will be conducted by study staff and used to assign participants to each arm/group condition using an algorithm before the baseline assessment. This randomization procedure ensures balance between groups on gender while also balancing total treatment numbers.*

### 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

*To evaluate the effects of our experimental manipulation, we need an active control group for this RCT study design. The HE has been used as a control condition in many previous published studies and is an accepted control intervention. Thus, we use it as a control condition in our study design. There are no known or potential problems associated with the control group.*

### 4.3 JUSTIFICATION FOR INTERVENTION

*The chosen 10-sessions of experimental manipulation - IBMT has been shown to improve behavior, cognition, and brain in previous RCTs in healthy adults. Thus, we choose to use the same setup and design, and expect the same length and frequency of the intervention would be appropriate for older adults.*

### 4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed the baseline assessment, 10 intervention sessions, post-assessment, and 3-month follow-up assessment.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

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

1. Provision of signed and dated informed consent form
2. Males and females; Age 40-65 years old.
3. Able to read/understand English
4. Normal performance using standardized cognitive tests
5. Self-reported decline in cognitive capacity such as memory loss
6. Eligible for non-invasive fMRI
7. Willing to be randomized
8. Free of any severe psychiatric diagnoses or medication that may affect participation

### 5.2 EXCLUSION CRITERIA

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

1. Medical disorders or medications that affect the central and autonomic nervous system; or a positive pregnancy test result (females)
2. Unable to provide consent or understand study procedures due to mental illness or cognitive limitations
3. Previous meditation experiences
4. Evidence of illicit drug use
5. Metal or metallic materials in the body such as pacemaker

### 5.3 LIFESTYLE CONSIDERATIONS

*N/A*

### 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria that are likely to change over time may be rescreened. Examples include the successful removal of metal devices that previously made them ineligible for an MRI scan. Rescreened participants will be assigned the same participant number as for the initial screening.

### 5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

*We anticipate to enroll 40 participants (males and females) ages from 40 to 65 years old across different race and ethnicity based on local demographic characteristics. Subjects will be recruited through print and media ads within local community. This will include radio and online ads and recruitment through social media. Flyers will be distributed throughout the local community. Based on our and other's previous experiences in longitudinal studies, about 5-10% of participants will dropout over the study period due to illness or relocation. We plan a dropout rate of 10% for this brief intervention. We propose to recruit 40 older adults of which 36 (90%) will complete the study.*

*Compensation and Retention. Participants will be financially compensated with $300 in total for completing the study protocol (approximately for 15 hours of time); participants who only partially complete the protocol will be compensated based on prorated hours. To maximize participant retention we will maintain contact with participants over time via frequent assessment intervals (e.g., requiring a functioning phone number and email address to contact participants by phone or email as needed, and obtaining the name, address, and phone number of at least 2 friends or classmates who can provide contact information for the participants, should we be unable to contact them during the study; emails and reminder phone calls prior to all study visits; offer flexible scheduling options for assessment (including weekends); provide fair compensation to participants; and maintain positive relations with participants. These procedures were used to maintain adequate participant retention in our prior NIH studies.*

## 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

*Experimental Manipulation – IBMT (Arm 1):* IBMT emphasizes the cooperation between body and mind in facilitating and achieving a meditative state ecologically. [1-7,18-22] Each IBMT session is facilitated by an experienced and certified coach who has demonstrated the ability to attain the appropriate state of body and mind, and to lead the group to achieve a similar state. The coach creates a harmonious and relaxed atmosphere, observes facial and body cues to identify those who are struggling with the method, and gives proper feedback for effective practice. IBMT coach helps subjects attain desired state by first providing a brief period to induce a cognitive or emotional state that will facilitate

the training. Then, coach helps subjects find an appropriate and balanced body posture and follow instructions to achieve deeper levels of relaxed body (physiology of relaxation) and experience a restful feeling and mental quiet (psychology of relaxation) mindfully.
When the mind wanders, the coach helps subjects accept and be open to experiences without judgment, and further guides subjects to use a favorite mental image as a tool to return to the present moment gently. At last, the coach facilitates a brief group discussion to ensure subjects having positive experiences consistent with the intent of IBMT. The method stresses no effort to control thoughts, but instead emphasizes a state of restful alertness that allows a high degree of awareness of the body, mind, and environment. [1-7,18-22]
*Control Intervention – Health Education (Arm 2): For HE, each session includes pre-, post- and practice sessions, similar to IBMT procedure and is facilitated by a trained coach. However, HE involves teaching participants different health promotion skills, behavior, attitude and strategies, which are guided by the certified coach. Participants have an active group experience that is not mindfulness-related. Therefore, HE induces a comparable but different experience and could serve as an ideal active control. Moreover, other groups have been using HE as active control in RCTs involving mindfulness intervention as an active control condition.* [2,7,64,65]

### 6.1.2 ADMINISTRATION AND/OR DOSING

*Both arms of interventions will be administered as a group by trained interventionists. Both interventions will have 10 consecutive group sessions, and the completion of all 10 sessions is considered to be having a "full-dose" intervention. Participants in the same arm/group will interact with a shared interventionist.*

## 6.2 FIDELITY

### 6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Explicit coach selection criteria and on-going monitoring and supervision of treatment delivery and fidelity will ensure that the interventions are of the highest quality, follow the protocols precisely, and prevent coach drift and contamination. For IBMT and HE, the coach must have a minimum of a master's degree in psychology, social work, or a related field and experience running group therapy. The coach will need to meet additional criteria: have completed the trainer course, had a daily practice of mindfulness, and attended a silent meditation retreat. To monitor coach's adherence and competence, all sessions will be recorded and a random sample of 10% will be rated by the investigators using the modified Adherence Scale to ensure the interventionist has adequate competence and adherence to the protocols, and to prevent drift.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

*To minimize potential biases, participants are randomized based on automatic covariate conducted by Co-I using an adaptive algorithm. Participants are blinded to the intervention. Specifically, they were told that they will be engaged in body-mind intervention, without knowing whether or not the intervention they received is the experimental manipulation or control intervention. See methods of analysis in* ***Section 9, Statistical Considerations*** *for details on randomization. Additionally, research staff who assesses participants are also blinded of the participants' intervention condition. Randomization code is maintained by different research staff. A planned breaking of randomization code and blinding would occur for any*

*participants who reported serious adverse events. The PI and Co-I will identify which group the participant is in, without the need for research staff to be involved in knowing the participant's intervention group.*

### 6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

*Participants' adherence with study procedures will be tracked by taking their attendance at intervention visits. Moreover, in each session, we use participant self-report and coach observation to calculate study intervention adherence by the participant based on their engagement and quality of practice.*

### 6.5 CONCOMITANT THERAPY

*N/A*

#### 6.5.1 RESCUE THERAPY

*N/A*

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

### 7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 1 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 1 week from the discontinuation date, the next scheduled assessment will not be administered. Thereafter, the participant will be not included in all future scheduled assessments, as they did not participate in the intervention.

### 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study

- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will not be replaced.

### 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 1 scheduled visit and study staff are unable to contact the participant after at least 3 attempts.

The following actions must be taken if a participant fails to return for a required study visit:

- The site will attempt to contact the participant, reschedule the missed visit within 1 week, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods).
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

*The study involves assessing participants at baseline, post-intervention, and 3-month follow-up. The participant will be screened for eligibility after consenting. They will fill out demographic questionnaires and MRI screening form to determine their eligibility. Next, they will undergo behavioral, cognitive, and brain assessments by trained research staff and/or MRI technician. All non-brain assessments will be conducted at PI's lab for all participants to decrease variability. All brain assessments will be conducted at Barrow Neurological Institute for all participants to decrease variability.*

*Below is a list and description of the assessments:*

- ***Performance-based assessments***
  *Cognitive assessments – N-Back working memory is a memory performance test*
- ***Administration of questionnaires, interviews***
  *Behavioral assessments – Emotional Regulation Questionnaire assesses emotion regulation, Five Facet Mindfulness Questionnaire assesses mindfulness, Subjective Cognitive Decline questionnaire assesses subjective report of cognitive decline*
- ***Imaging assessments***
  *MRI Scan – provides images of brain structure and function*

### 8.2 SAFETY ASSESSMENTS

*N/A*

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related***.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

*This protocol uses the definition of serious adverse event includes: (a) Death; (b) Hospitalization (initial or prolonged); (c) Life-threatening condition; (d) Disability or Permanent Damage; (e) Other Serious (Important Medical Events).*

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study

procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.

- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

#### 8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in medical care will be responsible for determining whether an adverse event (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 for the study procedures.

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

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (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 will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric 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.

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. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

PI will record 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, 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.

### 8.3.5 ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of an adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 24 hours after the investigator first learns of the event.

### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 24 hours after the investigator first learns of the event.

### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

*The PI will be responsible for reporting AEs or SAEs related to the study to participants as soon as possible, but* in no event later than 24 hours after the investigator first learns of the event.
*For incidental findings from MRI brain scan, the MRI facility will inform the PI if there is incidental finding and the PI will report the finding to participants as soon as possible, but* in no event later than 24 hours after the investigator first learns of the event.

### 8.3.8 EVENTS OF SPECIAL INTEREST

*N/A*

### 8.3.9 REPORTING OF PREGNANCY

*N/A*

## 8.4 UNANTICIPATED PROBLEMS

### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report 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 an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor/funding agency within 10 business days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 10 business days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 business days of the IRB's receipt of the report of the problem from the investigator.

### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

*The PI will be responsible for reporting UPs related to the study to participants as soon as possible, but in no event later than 10 working days after the investigator first learns of the UP.*

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s):

We hypothesize that, compared to participants who receive a control intervention, participants who receive IBMT for improving behavior and cognition will have improved working memory, emotion regulation, and reduced subjective report of cognitive decline after completing the intervention at post-assessment, and will continue to show improvement 3 months after the intervention. Alternatively, our null hypothesis is that there will be no difference in the effects of IBMT for improving behavior and cognition and those of control intervention at post-assessment or after 3 months of intervention.

- Secondary Endpoint(s):

We hypothesize that, compared to participants who receive a RT control intervention, participants who receive IBMT for improving brain function and structure will have improved white matter, grey matter, and functional connectivity in AD-signature regions after completing the intervention at post-assessment, and will continue to show improvement 3 months after the intervention. Alternatively, our null hypothesis is that there will be no difference in the effects of IBMT for improving brain function and structure and those of RT at post-assessment or after 3 months of intervention.

## 9.2 SAMPLE SIZE DETERMINATION

Our series of RCTs suggest that IBMT showed significant effects in relatively small sample size [1-44]. For example, a recent RCT in healthy older adults showed significant effects on quality of life (N=25) and in resting state functional connectivity and structural changes in the ACC/mPFC-Striatum networks following IBMT (N=13) [4]; In adults, we detected significant fMRI signal changes in the ACC/mPFC (Cohen's d= .90) after 10-session IBMT [9,11]. We used GPower 3.1 software to determine the smallest detectable effect for a treatment X time interaction term given various sample sizes and a power of 0.80, assuming varying correlations between repeated measures, which ranged from .30 -.60 on behavioral and .50 -.80 on fMRI measures in our prior studies [1-44]. Considering these factors, our target N of 40 after attrition will allow us to detect small-medium-sized effects on continuous outcomes. The N of 40 will provide a reasonable sample to determine the effect size of IBMT without utilizing an unreasonable amount of resources in this pilot. Specifically, 40 subjects will give us adequate statistical power (80%) to detect a medium effect size [f= 0.3 for ANOVA and h=0.6 for proportion difference] with alpha=0.05 for analysis proposed. This effect size is conservatively estimated based on our previous studies [5,8-12]. The Chi-square test would be less statistically powerful; however, as the nature of this project is exploratory, we are interested in determining the potential effect size of intervention and in developing our intervention protocol in older adults before testing it in a larger sample size.
Given the 1-year project with pre, post-intervention and follow-up and power considerations, the N of 40 we choose is also in line with our intervention cycles and capacities.

## 9.3 POPULATIONS FOR ANALYSES

The analysis population will be Modified Intention-to-Treat Analysis Population. Specifically, these participants are those who completed the full-dose of the intervention (10 sessions) and have complete and usable data for the primary endpoints.

## 9.4 STATISTICAL ANALYSIS PLAN

### 9.4.1 GENERAL APPROACH

Behavioral and brain data analysis will undergo separate analyzing streams to test intervention effects and underlying mechanisms at different time points. Given the scope of this 1-year pilot project, the logical first step at this early stage of research is to examine the potential intervention effects and mechanisms in small sample size, then move to the full scale RCTs for replication. To address our study Aims, repeated-measures ANOVA will be used. By utilizing all assessment points, this approach allows for well-powered tests to detect significant differences in changes across the experimental conditions, even when assuming smaller magnitude effect sizes. Effect size measures (from the repeated-measures ANOVA, Cohen's d highlighting mean differences between treatment and control groups across assessments) will also be calculated to describe the intervention's effect on study outcomes.

### 9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary endpoints are behavioral and cognitive assessments and are all repeated measures assessed at baseline, post-intervention, and 3-month follow-up. For cognitive assessment of N-Back working memory, percentage of correct trials will be calculated for each trial for all endpoints. For behavioral assessment of emotion regulation, mindfulness, and SCD, these self-report questionnaires will be calculated based on established scoring guides by summing all items within a given questionnaire for all endpoints. Next, the effects of intervention (IBMT vs. HE) on each of these primary endpoints will be examined using repeated-measures ANOVA with time x group interaction effect. Variance and covariance across repeated measures will be calculated as part of the ANOVA. Age and sex will be included as covariates to control for potential confounding effects of age and sex on behavioral and cognitive assessments. Results will be presented as F values for the interaction effect, along with p values to indicate statistical significance. Normality and homogeneity of variance assumptions will be checked using SPSS built-in tools for ANOVA. Because there are 4 primary endpoints, multiple comparison corrections will be conducted using FDR correction. Missing data will be handled with case-wise deletion.

### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints are brain assessments and are all repeated measures assessed at baseline, post-intervention, and 3-month follow-up. For brain assessment of white matter, white matter integrity metrics will be calculated for all endpoints based on standardized processing pipelines of diffusion-based white matter data using FSL (*http://www.fmrib.ox.ac.uk/fsl*). For brain assessment of grey matter, cortical thickness and volume metrics will be calculated for all endpoints based on standardized processing pipelines of structural MRI data using SPM12 (http://www.fil.ion.ucl.ac.uk/spm). For brain assessment of functional connectivity, pair-wise correlations of fMRI timeseries will be calculated for regions of interest and for all endpoints based on standardized processing pipelines of fMRI data using REST software (*www.restfmri.net*). After these data preprocessing and calculation, numerical values will be generated for all secondary endpoints (white matter, grey matter, and functional connectivity). Next, the effects of intervention (IBMT vs. HE) on each of these secondary endpoints will be examined using repeated-measures ANOVA with time x group interaction effect. Variance and covariance across repeated measures will be calculated as part of the ANOVA. Age and sex will be included as covariates to control for potential confounding effects of age and sex on brain function and structure. Results will be presented as F values for the interaction effect, along with p values to indicate statistical significance. Normality and homogeneity of variance assumptions will be checked using SPSS built-in tools for ANOVA. Because there are 3 secondary endpoints, multiple comparison corrections will be conducted using FDR correction. Missing data will be handled with case-wise deletion.

### 9.4.4 SAFETY ANALYSES

*N/A*

### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups will be compared on baseline characteristics including demographics, behavioral assessments of emotion regulation, mindfulness, and subjective cognitive decline, as well as cognitive assessment of N-Back working memory performance using independent samples t-tests.

#### 9.4.6 PLANNED INTERIM ANALYSES

*N/A*

#### 9.4.7 SUB-GROUP ANALYSES

Sub-group analyses will not be conducted for primary and secondary outcomes for this pilot study, as the sample size of sub-groups (N<10) based on age, sex, race/ethnicity or other demographic characteristic(s) will not be sufficient to conduct meaningful group analyses.

#### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

*Individual participant data will not be tabulated as the goal of the study is to examine group effects.*

#### 9.4.9 EXPLORATORY ANALYSES

*N/A*

## 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 intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol: Consent Form, see Section 12 Attachment.

##### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent will be administered by a member of the study team to the participant. The team member will give the participant a brief overview of the consent form and summarize relevant information from each section of the consent form. Participants will then be given time to read the consent form on their own. The study population involves English speaking cognitively normal adults, so no special procedures are needed to obtaining the consent. Participants will be asked if they understand and comprehend the consent form and if they have any questions. These procedures serve as means for determining competency and assessing comprehension/understanding of the participants. Any questions

the participants may have will be answered by the team member. Finally, participants are asked to indicate if they would like to enroll in the study or not by signing or not signing the consent form.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Pandemic, such as COVID-19

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

### 10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies, may inspect all documents and records required to be maintained by the investigator. The study site will permit access to such records.

The study participant's contact information will be securely stored at the study 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 the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to

share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the study site. After the study is completed, the de-identified, archived data will be transmitted to and stored at the study site's secured data storage space. The use of the de-identified data by other researchers including those outside of the study will be granted per reasonable requests.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| **Principal Investigator** | **Independent Data Safety Monitor** |
|---|---|
| *Yi-Yuan Tang, Ph.D., Professor* | *Elliot Stein, Ph.D., Investigator* |
| *Arizona State University* | *National Institute on Drug Abuse* |
| *425 N 5th St, Phoenix, AZ 85004* | *251 Bayview Boulevard Suite 200, Baltimore, MD 21224* |
| *4807903577* | *4437402650* |
| *yiyuan@asu.edu* | *stein@mail.nih.gov* |

### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including clinical trials and intervention. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data from each arm of the study. The DSMB will operate under

the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to NCCIH via annual report.

### 10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be conducted by the study site itself, so please see **Section 10.1.8, Quality Assurance and Quality Control.**

### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be implemented as follows:

**Informed consent ---** Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

**Source documents and the electronic data ---** Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

**Intervention Fidelity** — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

**Protocol Deviations** – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

### 10.1.9 DATA HANDLING AND RECORD KEEPING

#### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of study team at the site under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs) and SAEs will be entered into RedCap provided by the study site. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

#### 10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the study completion date. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

### 10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH 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 will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to NCCIH Program Official and NCCIH. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

### 10.1.11 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. Data from this study may be requested from other researchers 10 years after the completion of the primary endpoint by contacting PI Yi-Yuan Tang. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

### 10.1.12 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 NCCIH 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 ADDITIONAL CONSIDERATIONS

*N/A*

## 10.3 ABBREVIATIONS AND SPECIAL TERMS

| | |
|---|---|
| AE | Adverse Event |
| ANOVA | Analysis of Variance |
| CFR | Code of Federal Regulations |
| COC | Certificate of Confidentiality |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| fMRI | Functional Magnetic Resonance Imaging |
| HE | Health Education |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| HIPAA | Health Insurance Portability and Accountability Act |
| IBMT | Integrative Body Mind Training |
| ICH | International Council on Harmonisation |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| NCT | National Clinical Trial |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute or Center |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SOA | Schedule of Activities |
| UP | Unanticipated Problem |
| US | United States |

## 10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.0 | 02/10/2022 | Initial protocol | Initial protocol |
| 1.1 | 06/22/2022 | Added RAs to the study team, COVID screening | Modification |
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## 12 ATTACHMENT

# Consent Form: Bioscience

***Title of research study (clinical trial):*** *Modulation effects of a novel body-mind intervention on subjective cognitive decline*

***Investigator:*** *Dr. Yi-Yuan Tang, College of Health Solutions*

## *Why am I being invited to take part in a clinical trial?*

*We invite you to participate because you are healthy (free of any severe neurological and psychiatric diagnoses, having a self-reported cognitive decline) between 40 - 65 years old. Meanwhile, you are able to read/understand English and eligible for non-invasive fMRI, have normal or corrected-to-normal vision, weigh at least 110 lbs, and are willing to be randomized.*

## *Why is this clinical trial being done?*

*Cognitive decline may involve deficits in self-control networks and integrative body-mind training (IBMT) could improve self-control, which may help reduce cognitive decline. The purpose of this study is to investigate brain and body mechanisms and the effects of reducing cognitive decline following IBMT. This work will improve our understanding of how training may affect brain, performance and behavior, and we are hopeful that it will have an eventual impact of preventing and reducing cognitive decline in this group.*

## *How long will the clinical trial last?*

*We invite you to complete 5 onsite visits (each approximately 1 hour long). Visits will be scheduled roughly 1-6 months apart. The study is anticipated to spread across 12 months total (including 10 remote visits).*

## *How many people will be studied?*

*We expect about 120 people.*

## *What happens if I say yes, I want to be in this clinical trial?*

***It is up to you to decide whether or not to participate.*** *Consenting to participate in this study will take place remotely over Zoom or by phone, prior to engaging in research activities.*

*Eligibility Screen: you will be screened 5-10 min to make sure to meet the study eligibility criteria through Qualtrics or Redcap. If you meet criteria, you will be marked as "conditionally eligible" for study and move forward with the consent process on zoom. If not, participation in this clinical trial will stop at this time.*
*Consenting: You will meet with the research staff on zoom to review the study consent form.*
***There are 3 parts of this clinical trial:***
*Part 1. Survey and tasks: You will complete questionnaires and tasks related to cognition, emotion and health through Qualtrics or Redcap (about 60 min). If you have technical issues with Qualtrics or Redcap, we will guide you either via Zoom or in person.*
*Part 2. Five Brain MRI scans will occur at Barrow Neurological Institute (BNI) and consist of 5 visits about 1-6 months apart. For each of these visits, you will receive an MRI lasting no more than 60 minutes. During the MRI, you will be asked to watch a screen and complete some cognitive tasks or just close your eyes. You will interact with neuroimaging staff and Dr. Tang's study staff. This study does not aim to provide diagnosis, if MRI shows an abnormality, MRI technologist may suggest you see a doctor.*
*Part 3. Interventions: You will be randomly assigned to complete one intervention condition of this study (10 sessions with about 60 min/session). Interventions will be guided on zoom.*
*We will ask for your permission to contact you for future studies; however, this is not necessary to participate in the current project.*

## *What happens if I say yes, but I change my mind later?*

*You can leave at any time it will not be held against you. If you decide to leave, contact the investigator so that the investigator can terminate your participation. Already collected data may not be removed from the database.*

## *Is there any way being in this clinical trial could be bad for me?*

*There is very little risk to you for participation in this study including questionnaires, MRI and interventions. As part of the fMRI scan, you will be continuously monitored throughout the scan. If you have claustrophobia or a pacemaker or some metal objects in your body, you will not be allowed to be in this study because of the strong magnetic fields in the MRI scanner. Another risk is the possibility of metal objects being pulled into the magnet and potentially hitting you. To eliminate this risk, you will need to remove anything metal from your clothes, any metal piercings, and anything metal from your pockets. You will also walk through a metal detector (like airport scanners) when you come into the magnet chamber. It is important to know that no metal can be brought into the magnet room at any time. Once you are in the scanner, the door to the room will be closed so that no metal from outside accidentally goes near the magnet. If you are pregnant, you should delay your participation in this clinical trial.*

## *Will being in this study help me anyway?*

*We cannot promise any benefits to you or others from your taking part in this clinical trial, and do not anticipate any direct benefits to you. However, the overall goal of this clinical trial is to improve our understanding of how training may affect brain, performance and behavior. Thus, there is a potential benefit to improve brain function and change behavior such as reducing cognitive decline through information gained in this project.*

## *What happens to the information collected for the clinical trial?*

*Efforts will be made to limit the use and disclosure of your personal information to people who need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the Institutional Review Board and other representatives of this organization. The results may be used in reports, presentations, and publications but will not be reported back to you. If the results of the trial are published, your identity will remain confidential. For confidentiality purposes, your identity will be linked to a code number. A master list will be kept to link your name and the unique code number given to you. The master list, which contains your identity will be stored in secured computers and will be retained indefinitely. De-identified data collected as a part of the current clinical trial will not be shared with other investigators/industry sponsors for future research purposes.*

## *What else do I need to know?*

**ASU Lab COVID-19 Procedures:**

- We are required to do symptom checks 24-48 hours prior to your appointment and will also perform another symptom check and temperature check using a touchless thermometer upon arrival at the lab
- Lab disinfections are performed at the beginning and end of the lab work day by the research team and additional disinfections will be completed between your visits
- Both research team and you are required to wear masks when inside ASU building and withinASU community spaces, if you forget to bring one to your appointment, we can provide a disposable mask
- Only you will be permitted to enter the building. If needed, you may have one person accompany them to their appointments and will be subject to the same safety protocols.
- We will minimize the number of people in the lab at a given time. We plan to have two researchers in the lab with you – you face 1 researcher and 1 equipment faces 1 researcher
- You will be asked to wash your hands and/or use hand sanitizer throughout the appointment. Ahand sanitizing station is available in the lab

**ASU/BNI/Banner COVID-19 Procedures**

When conducting research visits at the Barrow Neurological Institute/Banner Health, all participants and research staff will be subject to/defer to the COVID procedures of the BNI Facilities, including, but not limited to temperature checks, COVID-19 health screening questionnaires, vaccination (when did you take vaccination and how many shots), etc. prior to entering the facility. Due to the nature of the assessments, the research team may need to be within 6 feet of the participant, for aperiod of time, for spotting purposes and/or to administer tests. To protect both the participant and research team,the following COVID procedures will be followed:

- Both research team and you are required to wear masks during the assessments.
- The research team plans to have no more than 3 research members present per visit, due to the different research specialty areas of the team, there may be two participant-facing researchers and one equipment-facing researcher.
- You will be asked to wash your hands and/or use hand sanitizer throughout the appointment.
- Equipment will be sanitized before and after use of each visit

This research is being funded by **the College of Health Solutions at ASU**. If you agree to take part in this research study, after completion, we will pay you **$300** for your time and effort. If you are getting more than $ 600 in

a calendar year through your participation in research studies at ASU, we will reach out to you for additional information. If you do not complete the study, the payment will be prorated based on the time of task completed. If you are not eligible for the study, you will not receive payment. If you agree to participate, then consent does not waive any of your legal rights. However, no funds havebeen set aside to compensate you in the event of injury. In the event of an injury or illness during any clinical evaluation, experimental session, or training session, 911 will be called and/or you will be directed to a nearby medical emergency facility. You will be responsible for the costs for any emergency services that are offered. If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information below. Any adverse event will be reported by the project PI to ASU IRB within 24 hours. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## *Who can I talk to?*

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the principal investigator 480-790-3577 (Yi-Yuan Tang), or yiyuan@asu.edu (Yi-Yuan Tang)

This clinical trial has been reviewed and approved by the Bioscience IRB ("IRB"). You may talk to them at (480) 965-6788 or research.integrity@asu.edu if:

- Your questions, concerns, or complaints are not being answered by the research team
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this clinical trial.

### Signature Block for Capable Adult

Your signature documents your permission to take part in this clinical trial.

| | |
|---|---|
| Signature of participant | Date |
| Printed name of participant | |
| Signature of person obtaining consent | Date |
| Printed name of person obtaining consent | |