PROTOCOL TITLE: Randomized Controlled Pilot Trial of Inspiratory Muscle Strength Training (IMST) to Reduce

Dementia Risk in Older Adults

NCT: 07349706

Date: 1.7.26

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VERSION NUMBER/DATE: 1/07.2025

Include the version number and date of this protocol.

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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PROTOCOL TITLE: Randomized Controlled Pilot Trial of Inspiratory Muscle Strength Training (IMST) to Reduce Dementia Risk in Older Adults

1.0 Study Summary

Study Title	Randomized Controlled Pilot Trial of Inspiratory Muscle Strength Training (IMST) to Reduce Dementia Risk in Older Adults
Study Design	2-arm Pilot RCT
Primary Objective	To evaluate the feasibility and preliminary efficacy of Inspiratory Muscle Strength Training (IMST) as a non-pharmacologic intervention to reduce cardiovascular and cognitive risks in older adults
Secondary Objective(s)	To examine secondary effects of IMST on mood, sleep quality, systemic inflammation, and physical/motor function. To assess adherence, acceptability, and feasibility of an 8-week home-based IMST protocol in a diverse older adult sample.
Research Intervention(s)/ Investigational Agent(s)	Inspiratory Muscle Strength Training (IMST) POWERbreathe® Electronic device
IND/IDE # (see section 5)	
Study Population	Adults aged 60-80 with cardiovascular risks for dementia
Sample Size	30
Study Duration for individual participants	~8 weeks
Study Specific Abbreviations/ Definitions	IMST = Inspiratory Muscle Strength Training

2.0 Objectives

2.1 The purpose of this study is to evaluate the feasibility and preliminary efficacy of Inspiratory Muscle Strength Training (IMST) as a non-pharmacologic intervention to reduce dementia risk factors in older adults. IMST has been shown to improve vascular health and may also benefit other modifiable risk factors for dementia, including cognitive function, sleep quality, mood, inflammation, and physical frailty.

Specific Aims:

- Aim 1: To evaluate the effect of high-resistance IMST on vascular risk factors for dementia.
- Aim 2: To assess the impact of IMST on executive functioning and related cognitive domains commonly affected in neurogenerative diseases.
- Aim 3: To examine secondary effects of IMST on mood, sleep quality, and physical/motor function.
- Aim 4: To assess adherence, acceptability, and feasibility of an 8-week home-based IMST protocol in a diverse older adult sample.

2.2 Hypotheses

Hypothesis 1: Participants in the high-resistance IMST group will show greater reductions in systolic blood pressure and other vascular health indicators compared to those in the sham IMST group after 8 weeks.
Hypothesis 2: Participants in the high-resistance IMST group will demonstrate greater improvements in executive cognitive function than those in the sham group.
Hypothesis 3: IMST will lead to secondary improvements in mood (reduced depression and anxiety symptoms), better sleep quality (as measured by self-report and actigraphy), and improved physical function (e.g., grip strength, gait speed).
Hypothesis 4: The IMST protocol will be feasible and acceptable, with at least 80% adherence to prescribed training sessions over the 8-week period.

3.0 Background

3.1 **Relevant prior experience and gaps in current knowledge:** Dementia is a growing public health challenge with no disease-modifying treatment. Prevention efforts increasingly focus on modifiable risk factors, including hypertension, poor sleep, inflammation, sedentary behavior, and cognitive underuse. Inspiratory Muscle Strength Training (IMST) is a novel intervention with demonstrated cardiovascular benefits, but its potential to target multiple dementia-related risk domains remains underexplored. To date, no study has evaluated the effects of IMST as a way to target multiple risk domains.

3.2 **Relevant preliminary data:** Prior work from our Co-I, Dr. Watso has demonstrated that IMST is effective in meaningfully reducing systolic blood pressure following 8 weeks of IMST intervention. Significant improvements in maximal inspiratory pressure were also evidenced. Further, IMST has been shown to be a relatively low-cost, time efficient, and low-risk intervention, making it ideal for older adults.

3.3 **Scientific background, rationale, and significance:** Vascular dysfunction is a key contributor to cognitive decline and dementia. IMST may reduce dementia risk by improving blood pressure, vascular reactivity, and cerebral perfusion. Additionally, IMST may benefit autonomic regulation, reduce

inflammation, and improve sleep—all of which are relevant to cognitive aging. This study is among the first to evaluate IMST across multiple dementia-related domains using both behavioral and biomarker outcomes. It will generate foundational data for future large-scale trials and inform the design of scalable, low-burden dementia prevention strategies accessible to diverse older adults.

4.0 Study Endpoints

4.1 The primary outcomes of this study are the change in laboratory-measured systolic BP and change in executive cognitive functioning measured using the NIH toolbox from baseline (week 0) to post-intervention (week 8) between the IMST (75% pressure) and IMST sham (15% pressure) groups.

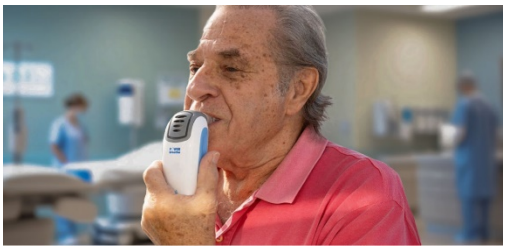
4.2 The secondary outcome of this study is to examine IMST effects on mood (depression and anxiety symptoms), sleep quality (PSQI and actigraphy), inflammatory markers (CRP, IL-6, TNF-α), and physical functioning (grip strength, gait speed, and sit-to-stand test).

4.3 In exploratory qualitative and quantitative analyses, we will examine adherence (self-report and device recorded) and acceptability of the IMST intervention via interview and 0-10 likert scales.

5.0 Investigational Test Articles or Products

5.1 Study Intervention Description

We will determine whether high-resistance IMST improves systolic blood pressure, executive functioning, sleep quality, systemic inflammation, and physical/motor function in older adults at risk for dementia. We will use POWERbreathe® Electronic IMST devices and manually set them to 75% or 15% of an individual's IPpeak, depending on their randomization, to the high-resistance IMST group or very low-resistance IMST (sham) group. All participants will complete 30 training breaths per day at home for 8 weeks, which will be confirmed through visually inspecting the stored device training history during in-person assessments, as well as via regular check-ins with participants for compliance.



5.2 Drug/Device Handling

All devices will be stored in the Center for Translational Behavioral Science and handled by the study team who are authorized investigators involved with this project. The Fitbit and IMST devices will be provided to participants only after they have been familiarized and provided with instructions for safely using the devices. Notably, the IMST device is commercially available and has been safely used in numerous research studies among a variety of populations. To operate the device, participants simply inhale against the device mouthpiece. We will install the Fitbit mobile app on participant devices or laboratory iPads to sync participant Fitbit data on a daily and/or weekly basis during weekly in-person assessments. If a participant does not have a smartphone or declines to download the Fitbit app, data will be synced on a weekly basis to the laboratory iPad.

Participants will be required to return the POWERBreathe and Fitbit devices upon study completion, or upon drop-out/withdrawal from the study. The POWERBreathe will be sanitized, cleaned, and reissued to new participants once returned, consistent with prior protocols.

6.0 Procedures Involved

7.1 Study design. A total of 30 participants will be recruited for the trial, with approximately equal number of individuals randomly assigned to one of two groups (75% vs 15% maximum inspiratory pressure(MIP)) using a randomization software. An 8-week intervention period was chosen based on prior research. Extended in-person assessments will be completed at baseline and 8-weeks (post intervention). Additionally, participants will come to the laboratory once a week to have device settings adjusted, sync Fitbit data, and complete brief assessments of vitals, mood, and well-being.

6.2 Research Procedures

Recruitment efforts will take place on a rolling basis until an N of 30 is achieved. Currently, the PI's laboratory includes a participant registry of ~500 individuals aged 40+ that are interested in being contacted for research. Thus, participants will be recruited via email and phone contact from the laboratory participant registry. Recruitment efforts will also include collaboration with local community-based organizations and institutions, (e.g., social service providers, faith-based institutions, healthcare providers, elder/aging advocacy organizations, senior centers, etc.) through community outreach such as posting flyers and in-person recruitment.

Preliminary screening
Potential participants will be provided with a brief overview of the study and, if still interested, complete a telephone screening or be scheduled for a later date. Eligibility will be based on inclusion/exclusion criteria and responses to questions about medical history. Screening documentation will include identifiable information including name, email, and telephone number, and, therefore, will be kept in a locked cabinet and/or password-protected folder.

An initial telephone screening will include the telephone Montreal Cognitive Assessment (tMoCA), the Memory Complaint Scale (MCS), and a self-reported version of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score. Additionally, questions about basic demographics, health conditions (e.g. unstable cardiovascular or pulmonary disease), medications, and major psychiatric illnesses will be included in the telephone screener. Inclusion criteria are: 1) Ages 60-80; 2) converted telephone MoCA total score≥18; 3) presence of at least one dementia risk factor (e.g., MCI or subjective cognitive decline, hypertension [SBP >130 mmHg or on medication], sedentary lifestyle [<150 min/week], family history of dementia or self-reported APOE ε4 carrier, or mild sleep-disordered breathing; CAIDE total score [>5]; (4) capable of independently completing or requiring minimal assistance with inspiratory muscle strength training (IMST); and (5) willing to adhere to the IMST protocol (approximately 5–10 minutes per day for 8 weeks). Optional inclusion of inspiratory muscle weakness (MIP <80 cmH_2O for men, <70 cmH_2O for women) will also be assessed. Participants will be excluded if any of the following are endorsed: 1) tMoCA <18, or diagnosis of neurodegenerative illness at the discretion of principal investigator (except MCI*); 2*) current evidence of any major psychiatric disorder including psychosis (at the discretion of principal investigator), bipolar disorder, severe major depression (PHQ-9 > 20); 3) unstable cardiovascular or pulmonary disease; 4) recent respiratory therapy or major medication changes; 5) self-reported severe untreated obstructive sleep apnea (OSA); 6) recent use (within the past 3 months) of CPAP, BiPAP, or inspiratory muscle training; 7) lung and eardrum injuries, and 8) Non-English speaking. Participants with a pacemaker or other medical implants

containing magnets or electronics will be noted on REDCap and excluded from body composition analyses.

Consent

Based on the screening, eligible participants will be contacted by a qualified member of the research team to perform the informed consent over Zoom or in-person. The study team member will share their screen (or iPad screen) and review each section of the consent form in detail with the participant. At the end of the consent meeting, participants will be asked to provide a description of their participation in the study in their own words to check comprehension. Participants will then be asked to provide an electronic signature to participate. If participants choose to complete an in-person consent, they may opt to schedule their baseline appointment immediately following consent to reduce study-related travel.

Baseline

Consented participants will be scheduled to come in-person for an approximately 2-3 hour visit at the Center for Translational Behavioral Science (CTBScience) suite that will occur prior to beginning use of the IMST device. The assessment will consist of 1) basic vitals and biometrics assessment (BIA), 2) urine assessment (hydration), 3) a fasting blood draw for a lipidPlus panel and inflammatory biomarkers, and point-of-care HbA1c testing (completed by a trained phlebotomist), 4) skin carotenoid assessment 5) a brief clinical interview and measures of socio-emotional functioning (e.g., mood, physical activity, sleep), 6) self-reported health assessments, 7) cognition and motor assessments using the NIH Toolbox Motor Battery, NIH Toolbox Cognitive Battery, and 30-second sit-to-stand test (30-s CST), and 8) an initial training session for IMST. Survey items will be administered via REDCap using a laboratory iPad, while the NIH toolbox will be administered by a trained research assistant. The NIH Toolbox Motor Battery will consist of a 4-meter walk gait speed test, a grip strength test, and 9-hole pegboard dexterity test. All participants will receive actigraphy monitoring device (Fitbit) for at-home use. The *attached Baseline checklist* may be administered in a different order than listed based on participant and research assistant factors (availability or any unique circumstances that may arise).

Participants will be asked to avoid caffeine, alcohol, and vigorous exercise for 24 hours before each assessment. Participants will be asked to bring in their medication list. Trained research assistants will measure in-laboratory ambulatory blood pressure using automated monitors (average of 3 readings). We will collect venous blood via a standard needle stick to measure circulating biomarkers. Blood samples collected will be approximately 10mL per visit for a final total of 20mL (for context a blood donation is 32 tablespoons. We will assess body composition using a commercially available Mediana i55 body composition analyzer. We will assess physical activity habits with a validated questionnaire during each visit. We will evaluate sleep quality, depression and anxiety, perceived stress, and adherence. See attached *list of measures* for more information.

We will assess inspiratory muscle strength using the POWERbreathe® electronic device in the laboratory. We will use a validated dyspnea scale. Participants will complete an initial training session using IMST in the laboratory under trained RA supervision. Participants will use the POWERbreathe® IMST device and perform up to six maximal inhalations in the laboratory to determine their MIP. Participants will complete an additional 30 inhalations in the laboratory as their initial training session. See attached participant instructions for more information. Research assistants assigned to set the workload for the IMST devices will not be involved in primary data analyses. All data processing will be completed while researchers are blind to participant group.

Intervention Procedures

Participants will complete 30 training breaths per day (approximately five minutes per day) at home, which will be confirmed via the stored device history and a paper log collected during weekly in-person check-ins with participants. A minimum of 5-days/week of IMST use will be considered high adherence. Participants will be instructed to complete these in the morning for consistency. Individuals will be instructed to not make dietary changes throughout their participation, which will be confirmed via 24-hour food recall during each time point and weekly check-in. Participant stored device history will be assessed to ensure compliance during weekly check-ins. Participant devices will be cleaned and sanitized during weekly check-ins.

Participants will be asked to wear the actigraphy monitoring device (Fitbit) every day except when charging to assess steps, heart rate, and monitor sleep.

Weekly Tracking

Participants will complete weekly in-person check-ins with study team members. These visits will consist of 1) basic vitals, 2) body composition analysis, 3) a urine gravity test, 4) mood and sleep questions, and 5) self-reported health and nutrition surveys, and 6) skin carotenoid assessment. Survey items will be administered via REDCap using an iPad. Participants will be asked to bring in their medication list.

8-Week Post Assessment

After completing 8 weeks of IMST use, the study team will evaluate IMST adherence based on daily use measured by the device, a paper log kept by the participant, and acceptability using a 0-10 scale. All participants will repeat all procedures from baseline (e.g. questionnaires, NIH Toolbox, a fasting blood draw for cardiometabolic outcomes and point-of-care HbA1c testing), excluding the IMST training session and clinical interview. Participants will be asked to bring in their medication list. Participants will complete a semi-structured exit interview to collect qualitative data on their experience using the IMST device. Study team members will sync the remaining Fitbit data using the app on the laboratory iPad during this visit. Participants will receive a post participation debrief statement after all procedures have been completed.

Pre-Screening	Potential participants recruited from the Integrative Science for Healthy Aging registry will be provided with a brief overview of the study and, if still interested, be pre-screened to determine eligibility before scheduling their telephone screening. Eligibility will be based on inclusion/exclusion criteria and responses to questions about medical history.
Phone Screening	An initial telephone screening will consist of a ~30-minute phone call. The telephone screening will include the telephone Montreal Cognitive Assessment (MoCA), the Memory Complaint Scale (MCS), and a self-reported version of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score. Additionally, questions about basic demographics, health conditions (e.g. unstable cardiovascular or pulmonary disease),

	medications, and major psychiatric illnesses will be included in the telephone screener.
Consent	Eligible participants will be contacted by a qualified member of the research team to perform the informed consent over Zoom or in-person (if requested).
Baseline	The first appointment will consist of an in-person, approximately 2-3 hour visit at CTBScience that will occur in the day prior to beginning IMST. The appointment will include basic vitals, body composition analysis, a urine gravity test, a fasting blood draw and point-of-care HbA1c testing (completed by a trained phlebotomist), a brief clinical interview, mood and sleep questions, self-reported health surveys, a thinking and memory test, a set of movement and coordination tests, an initial training session for IMST device, and a brief hand-squeezing exercise. All survey items will be completed using an iPad, while the interview and the movement test will be completed by a trained research assistant. Participants will receive an actigraphy monitoring device (Fitbit) for at-home use. Participants will be paid $60 for their time.
Week 1 – Adjustment Visit/Check-in	Participants will come in-person for their week 1 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
Week 2 – Adjustment Visit/Check-in	Participants will come in-person for their week 2 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
Week 3 – Adjustment Visit/Check-in	Participants will come in-person for their week 3 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
Week 4 – Adjustment Visit/Check-in	Participants will come in-person for their week 4 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
Week 5 – Adjustment Visit/Check-in	Participants will come in-person for their week 5 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey

	items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
Week 6 – Adjustment Visit/Check-in	Participants will come in-person for their week 6 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
Week 7 – Adjustment Visit/Check-in	Participants will come in-person for their week 7 adjustment visit for ~25 minutes. The visit will consist of basic vitals, body composition analysis, a urine gravity test, skin carotenoid, mood and sleep questions, and self-reported health surveys. All survey items will be completed using an iPad. Fitbit data will be synced. Participants will be paid $15 for their time.
8-Week Post Assessment	On the 8th week of the study, participants will be asked to come in-person to CBTScience for an approximately 2.5-hour visit. Participants will repeat all tests from baseline (e.g., health and mood questions, a set of movement and coordination tests, a brief hand-squeezing exercise, skin carotenoid, a fasting blood draw and point-of-care HbA1c testing), excluding the interview. Urine specific gravity will also be tested. Participants will be asked to complete an interview about their experience using the device. Participants will be asked to return the IMST device and the Fitbit during this appointment. Participants will be paid $60 *contingent on returning the devices.*

6.3 Risk Mitigation:

To reduce potential risks, all participants must meet the inclusion criteria to participate in this research study. Potential subjects will be asked screening questions related to their demographics and medical history to assess general health. Participants will be given the option to end participation in the study at any time with no penalty for doing so. Participants may take breaks from testing as requested or choose not to answer sensitive questions. Research staff continually monitor the well-being of each participant via in-person assessments with a specific question about the onset of new health symptoms, which alerts the PI immediately if endorsed.

During the inspiratory muscle training and testing, participants will be instructed to slow down their rate of breathing or take a break should they feel lightheaded or dizzy during use – and to sit down if this does not immediately subside. We will instruct individuals to abstain from using the device if symptoms of a cold, sinusitis, or a respiratory tract infection are present. We will instruct participants to stop training and immediately notify us if any mild ear discomfort increases in severity or frequency. To minimize the risk of infection, participants will only use a brand new and/or fully sterilized (per company guidelines) mouthpiece/valve headpiece. We will instruct individuals to stop training and immediately notify us if there is pain present while training.

During blood draws, participants may experience discomfort, bleeding, and/or bruising, and on rare occasions, a person may feel dizzy or faint. Participants might feel mild temporary discomfort during handgrip exercises and when the cuff is inflated. All procedures will be conducted by trained research staff.

Participants will be monitored by the study team on a weekly basis to assess any adverse response. Participants will also be encouraged to reach out to the study team if new health symptoms arise during the study. If a significant adverse response is reported or identified, the PI will immediately review the symptoms, onset, course, and severity to determine next steps. All AEs will be reported to the IRB.

Participants will be monitored by the study team during in-person assessments to assess suicide and self-harm risk. Automated alerts through REDCap will notify the investigative team and the PI immediately if a participant is flagged as at risk based on the PHQ-9. The Principal Investigator (a licensed clinical psychologist and board-certified geropsychologist) will conduct a risk assessment within one business day and determine whether further clinical action or referral is warranted. Participants deemed not at moderate or high risk will be cleared without additional intervention. Risk will be classified based on the Joiner et al., 1999 and Chu et al., 2015 criteria.

7.0 Data and Specimen Banking

All data will be collected using a laboratory iPad (not connected to the cloud) and will be stored in REDCap. All surveys and participant data collected in-person will be directly entered into REDCap by participants, or a research assistant will enter this data for participants. Once data is entered and double-checked, physical copies along with checklists and other notes will be stored in a locked file. All physical data will not include identifiable information and will only use a coded ID. These will be stored in a locked file drawer in the PI's laboratory at the Center for Translational Behavioral Science suite.

Blood samples will be collected by a trained phlebotomist in the phlebotomy lab at the Center for Translational Behavioral Science. Samples will be labeled and identified only by an ID number. These samples will be used to assess LipidPlus panels and inflammatory biomarkers of participants. Samples will be stored in a -80 F freezer in the phlebotomy lab. Panels will be analyzed using a Piccolo Xpress Chemistry analyzer in the Center for Translational Behavioral Science. Once results of the panels are returned, this data will be entered into REDCap and stored with other participant data (described below). Coded biological samples may be analyzed by other IRB approved team members for secondary analyses and will be disposed of once depleted via analyses. Urine samples will not be retained.

Data for Future Use: Participants consent to these procedures as part of the consent process. Data collected during this research study may be used for future research purposes. After the study is complete, the data stored will be de-identified. De-identified Data that cannot be linked to participants will be kept indefinitely; this data will be saved for future use and may be shared with other researchers. This data may be used for secondary data analysis to inform future publications examining late-life health and cognition, as well as preliminary data for future grant applications.

At the end of the study data collected may be made available, in accordance with the NIH Data Sharing Policy (http://grants.nih.gov/grants/policy/data_sharing). This data will be saved for future use and may be shared with other researchers. By participating in this study, participants are agreeing to allow us to save and share their data anonymously for research purposes. We will ask consented participants if they wish to be contacted for future research opportunities and to be kept up-to-date on relevant information, resources, and news via an email newsletter. On the study consent form, we ask participants if they wish to be contacted about future research opportunities in which they might be eligible. For this study, information retained for individuals that give permission to keep their contact information for future research opportunities will include: Names, Email addresses, mailing address, and Working phone number. This information will be collected using a secure REDCap form, only accessible by the study team. Contact information will be stored and maintained in a password protected excel file and will be kept separate from individual study related information. Access to this information will be limited to only designated study team members throughout the duration of the study. The study team will carefully review and document which participants granted permission for the study team to retain their information. Participants who say "yes" will have their information stored in a password-protected file, separate from the study data, and accessible to only trained members of the study team. Participants may request to be removed from the mailing list at any time, in which case a note will be made for data cleaning to remove that individual when data is cleaned. See protocol STUDY00003815 for additional information about this participant repository.

8.0 Sharing of Results with Subjects

8.1 When results are published or discussed at conferences, no information will be included that will reveal the identity of the participants. Participants have the opportunity to receive the results of the cognitive, body composition, and blood biomarker analyses from their assessment visits at the end of the trial. Participants may request to obtain study results to bring to their physician.

9.0 Study Timelines

Participants will be in the study for approximately 8-weeks if they complete all visits (i.e., baseline through 8-week post-assessment). The duration to enroll all study participants is anticipated to take approximately 5 months. It is anticipated to take up to another year to complete primary analyses for this study.

10.0 Inclusion and Exclusion Criteria

Screening

Potential participants will be provided with a brief overview of the study and, if still interested, complete their telephone screening or schedule for a later date. Eligibility will be based on inclusion/exclusion criteria and responses to questions about medical history. Initial screening documentation will include identifiable information including name, email, and telephone number, and, therefore, will be kept in a locked cabinet and/or password-protected folder.

An initial telephone screening will include the telephone Montreal Cognitive Assessment (MoCA), the Memory Complaint Scale (MCS), and a self-reported version of the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score. Additionally, questions about basic demographics,

health conditions (e.g. unstable cardiovascular or pulmonary disease), medications, and major psychiatric illnesses will be included in the telephone screener. Inclusion criteria are: 1) Ages 60-80; 2) converted telephone MoCA total score≥18; 3) presence of at least one dementia risk factor (e.g., MCI or subjective cognitive decline, hypertension [SBP >130 mmHg or on medication], sedentary lifestyle [<150 min/week], family history of dementia or APOE ε4 carrier, or mild sleep-disordered breathing); (4) capable of independently completing or requiring minimal assistance with inspiratory muscle strength training (IMST); and (5) willing to adhere to the IMST protocol (approximately 5–10 minutes per day for 8 weeks). Optional inclusion of inspiratory muscle weakness (MIP <80 cmH_2O for men, <70 cmH_2O for women) will also be assessed. Participants will be excluded if any of the following are endorsed: 1) tMoCA <18, or diagnosis of neurodegenerative illness at the discretion of principal investigator (except MCI*; 2*) current evidence of any major psychiatric disorder including psychosis (at the discretion of principal investigator), bipolar disorder, severe major depression (PHQ-9 > 20); 3) unstable cardiovascular or pulmonary disease; 4) recent respiratory therapy or major medication changes; 5) self-reported severe untreated obstructive sleep apnea (OSA); 6) recent use (within the past 3 months) of CPAP, BiPAP, or inspiratory muscle training; 7) lung and eardrum injuries and 8) Non-English speaking.

11.0 Vulnerable Populations

Our screening and consent procedures will identify and exclude adults (60-80) unable to provide informed consent independently. Individuals will be screened and excluded for a diagnosis of a major neurocognitive disorder. Only cognitively normal and individuals with mild cognitive impairment will be included. Of note, a mild neurocognitive disorder (MNCD) also known as MCI is characterized by slight decline in cognitive functioning, which require compensatory strategies to retain independence. Individuals with MNCD are able to live and function independently and are able to provide consent to participate. The PI is a licensed clinical psychologist with board certification in geropsychology and will rule out individuals who do not have capacity to consent via a telephone cognitive screener. To further ensure participants are able to provide consent, the consent form will be written at an 8th grade level and will include comprehension questions before signing to ensure that the participant understands their involvement in the study.

12.0 Local Number of Subjects

We expect to screen approximately 100 participants to identify and enroll 30 eligible participants.

13.0 Recruitment Methods

Recruitment efforts will take place on a rolling basis until an N of 30 is achieved. Currently, the PI's laboratory includes a participant registry of ~500 individuals aged 40+ that are interested in being contacted for research. Thus, participants will be recruited via email and phone contact from the laboratory participant registry. Recruitment efforts will also include collaboration with local community-based organizations and institutions, (e.g., social service providers, faith-based institutions, healthcare providers, elder/aging advocacy organizations, senior centers, etc.) through community outreach such as posting flyers and in-person recruitment.

In total, participants may complete a telephone screening ($5), two in-person assessments ($60 each), and seven in-person check-ins ($15 each). Thus, participants completing all aspects of the study may receive a total of $230 in research-related compensation. In-person assessments will be paid in cash, and telephonic screenings will be paid through email or at in-person assessments

in the form of a gift card or cash. Participants will be compensated for all study related assessments they complete at least 80%, *contingent on return of study devices*.

14.0 Withdrawal of Subjects

14.1 Participants can be withdrawn from the study if they are not following instructions, the investigator decides that continuation could be harmful to the participant, the participant needs treatment not allowed in this study, the study is canceled, or for other administrative reasons.

14.2 Participants will be contacted through their provided contact information and informed of their termination from the study. The reason(s) will be thoroughly explained to each participant, and any further questions will be answered.

14.3 Any data already collected from the withdrawn subject will be retained and used in the final analysis.

15.0 Risks to Subjects

15.1 Risks

Peripheral intravenous butterfly needle/catheter and blood samples:

Less Likely

In 100 people, approximately (2 to 20 individuals) may have:

- Mild risk: You may have discomfort, temporary bleeding, redness, mild swelling, and/or bruising.
- Mild risk: You may feel dizzy or faint.

Rare

- We carry out several precautions to ensure that any of your health information, such as biomarkers related to blood pressure control, is kept coded and de-identified when analyzed.

Of 10,000 people, approximately (1 or less) may have:

- Serious risk: An infection
- Serious risk: A blood clot or breakage of the catheter (very low risk)

Lancet (Fingerstick) and Capillary Blood Samples:

Less Likely

In 100 people, approximately (2 to 20 individuals) may have:

- **Mild risk:** You may have brief discomfort or stinging, temporary bleeding, redness, mild swelling, and/or bruising.
- **Mild risk:** You may feel dizzy or faint.

Rare

Of 10,000 people, approximately (1 or less) may have:

- **Serious risk:** An infection.
- **Serious risk:** Scarring at the puncture site (very low risk).

Mental health assessments/surveys

Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may refuse to answer any of the questions, take a break, or stop your participation in this study at any time.

Respiratory training and pulmonary function assessments

You may have slight soreness in your breathing muscles (around your rib cage and your neck) during/after the eight weeks of training and/or during/after the pulmonary function assessments. Also, you should slow down your rate of breathing or take a break if you feel lightheaded or dizzy during at-home respiratory training – and sit down if this does not immediately subside. You should abstain from using the device if symptoms of a cold, sinusitis, or a respiratory tract infection are present. You should stop training and immediately notify us if any pain develops.

Loss of Confidentiality:

There is a slight risk that information collected about participants could be revealed inappropriately or accidentally. Taking part in this research involves providing information that is considered confidential or private. Efforts such as coding research records, keeping research records secure, and allowing only authorized people to have access to research records, will be made to keep volunteer information safe. All data and specimen samples will be labeled with a unique series of numbers. If samples will be transmitted outside Florida State University, all identifying information will be removed from the samples before they are released to any other investigators. Researchers will take appropriate steps to protect any information collected.

Additionally, if the study team determines you may be at risk of self-harm or suicide, the study team will be required to share this information and refer you to appropriate follow-up care or support services.

Unknown Risks:

In addition to the risks listed above, participants may experience a previously unknown risk or side effect.

All unexpected serious adverse events will be immediately (within 24 hours) addressed and reported to the IRB. In accordance with the FSU Investigator Manual, the PI will complete the Report New Information SmartForm within 5 business days for any of the following information items: information that indicates a new or increased risk, or a new safety issue; harm experienced by a subject or other individual, which in the opinion of the investigator are unexpected and probably related to the research procedures (will be reported within 24 hours if a unexpected serious adverse event); non-compliance with the federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance; audit, inspection, or inquiry by a federal agency and any resulting reports; written reports of study monitors; failure to follow the protocol due to the action or inaction of the investigator or research staff; breach of confidentiality; change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a subject; incarceration of a subject in a study not approved by the IRB to involve prisoners; complaint of a subject that cannot be resolved by the research team; premature suspension or termination of the protocol by the sponsor, investigator, or institution; or unanticipated adverse device effect (any unanticipated serious adverse device effect will be reported within 24 hours). The PI, co-investigators, and research staff will protect the rights, safety, and welfare of subjects involved in the research.

16.0 Potential Benefits to Subjects

16.1 Participants may experience improvements in markers of health as a result of the intervention (particularly in the high-resistance training study arm). However, no benefit from participation in this study is guaranteed. The final results of the study will not be available until all analyses are completed. This may take up to five years.

17.0 Data Management and Confidentiality

17.1 See section 4.1.

17.2 De-identified data collected will be securely stored in a filing cabinet and/or password-protected folder in our laboratory. Questionnaires completed online will not be linked to identifiable information and will only be accessible by team members who have been granted access by the project PI. All data will only be accessible to the PI and study team. The data will be linked to subjects via codes to ensure their protection and confidentiality; the codes will not include HIPPA identifiers, such as initials, etc. The encryption code for participants will be kept in a password-protected folder. Research staff will be trained on the importance of participant confidentiality.

17.3 Efforts will be made to limit the use and disclosure of personal information, including research studies and medical records, to people who need to review this information. If identifiers are removed from the identifiable private information that is collected during this research, that information or those samples could be used for future research studies or distributed to other investigators for future research studies without additional informed consent. Published results of this study will not report any identifying information. A description of this clinical trial will also be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify the participant. At most, the website will include a summary of the results.

17.4 Data and specimens will be handled safely and will be coded, as indicated in previous sections of this protocol, by trained study team members. See section 7.0.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

18.1 Alerts will be generated by REDCap for certain items indicating a potential adverse event or elevated suicide risk. Additionally, during weekly laboratory meetings, we will discuss any potential harms/benefits observed with pertinent data. Should any potential harms become apparent, we will follow IRB reporting guidance while, in parallel, maintaining a strong line of communication with a study nurse. Safety information will be recorded based on observations from the data and/or participant reports. The PI (Julia Sheffler, PhD, ABPP) along with pertinent study team members (e.g., a nurse) will review safety information.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Any personal information collected during screening and study visits will be kept private and confidential. Participants will be reassured that all necessary precautions and procedures are being taken to protect their privacy and interactions.

19.2 Participants will be informed of the main objectives of the study and the rationale for each procedure being performed. Participants will also be informed of the strict confidentiality policies regarding data storage and protection. The PI or study team will inform the participants of the rationale for the health history questionnaire and that the questions are in place to ensure their safety.

19.3 All data collected in hardcopy will be stored and locked in a filing cabinet. Only the PI and study team will have a key to access the locked filing cabinet. All the data collected in softcopy will be stored in password-protected folders. The PI and study team will have access to electronic data that does not include any personally identifiable data, such as initials.

20.0 Compensation for Research-Related Injury

20.1 Florida State University has no program to pay for medical care for research-related injuries. In the case of unforeseeable risks occurring, medical care will be made available to the participant. This care is not covered by the university and will be billed to the participant, their insurance, or other third parties.

21.0 Economic Burden to Subjects

21.1 Participants are responsible for transportation to and from the CTBScience suite at Innovation Park.

22.0 Consent Process

Our screening and consent procedures will identify and exclude adults (60-80) unable to provide informed consent independently. Individuals will be screened and excluded for a diagnosis of a major neurocognitive disorder.

Consent will be obtained following the "SOP: Written Documentation of Consent (HRP-091)." Participants will review the consent document via video call through HIPAA Compliant Zoom or on an iPad at the Center for Translational Behavioral Science with a research team member prior to providing an electronic signature. The consent form will be written at an 8th grade level. The research team member will provide information on the purpose of the study, the procedures involved, risks, and expectations and requirements to participate in the study. The research team member will review comprehension questions about the study to ensure that the participant understands their role and the extent of the study before providing consent. Participants will be provided a signed copy of the consent form to their email once completed. Please see attached consent document for more details. Participants will be notified of any changes to the consent form affecting their participation in the study via telephone call and will check "approve" or "deny" for continued participation based on changes.

23.0 Process to Document Consent in Writing

Our consent process will follow the "SOP: Written Documentation of Consent (HRP-091)." However, all consent processes will be documented electronically, rather than using a physical copy. The full consent form (see attached) will be reviewed with the participant via HIPAA Compliant Zoom or in-person by a trained research team member. Participants will be asked to electronically sign and date the consent form only after they have reviewed the form with the researcher, have demonstrated their understanding of the research procedures, and have had an opportunity to ask questions about the study. Documentation of consent will be stored electronically using the FSU REDCap platform.

24.0 Setting

The research team may engage in recruitment activities in a variety of community settings as permitted. Although most participants will be recruited telephonically using existing registries and databases, participants may be recruited through flyers, community talks, and participation at community events.

Currently, the IMST will be administered at home independently by research participants.

All data will be collected using either online surveys emailed to participants, or in-person at FSU's Center for Translational Behavioral Science (2010 Levy Ave, Building B, Suite 0266). Data will be stored in a secure office and in a locked cabinet in this suite until it is entered in REDCap.

25.0 Resources Available

The Integrative Science for Healthy Aging program, led by Dr. Julia Sheffler, has dedicated laboratory space containing neuropsychological testing rooms, phlebotomy/biological sample collection and storage space, and workspaces for research assistants. The PI has a private office in the CTBScience suite with a dedicated, password-protected desktop and laptop computer with software needed to analyze and publish data relevant to the proposal. The office is also equipped with other necessary equipment (iPad, telephone, printer, scanner, secure file storage, etc.). The PI's laboratory has all the equipment needed to complete the proposed project. The PI's office is close to the waiting room, participant rooms, and workstations for research assistants. These workspaces are conveniently located off FSU main campus for easy participant parking and access.

As previously noted, recruitment and retention of the target sample is highly feasible based on prior clinical trials in the PI's laboratory. The PI maintains a staff of trained RAs who complete rigorous training procedures and documentation of training before they begin seeing research participants. The PI's laboratory also includes a full-time research coordinator, Naomi Frederic, who is trained in all procedures and provides additional oversight and a resource for training RAs. Random quality control assessments will be completed by the research coordinator during study assessments, to ensure that RAs are completing the checklist of procedures with fidelity. Multiple research assistants in the PIs laboratory have been trained as phlebotomists following procedures recommended by the office of clinical research. One experienced research assistant, who is a certified medical assistant (Trinity Sims), acts as the lead phlebotomist who assists in overseeing training and onboarding of new phlebotomists following the laboratory's standardized procedures. Procedures include: completing required trainings through FSU (e.g., bloodborne pathogens training, hazardous waste), shadowing current phlebotomists, practicing initial draws using a practice manakin arm, practicing with other research assistants, and completing a final "check-out" on a volunteer RA. The new phlebotomist's first blood draws with participants are always supervised by an experienced phlebotomist until the lead phlebotomist and PI determine they are ready to independently complete blood draws.

This project will be funded by the PI's startup funds provided either by a U54 NIH grant or funds provided by the university.

26.0 Multi-Site Research

N/A