Clinical Intervention Study Protocol

NCT03859076

FULL PROTOCOL TITLE
Mindfulness-Based Blood Pressure Reduction: Stage 2a RCT

Study Chairman or Principal Investigator:
Eric B. Loucks, PhD
Associate Professor, Department of Epidemiology
Brown University School of Public Health

Supported by:
The National Center for Complementary and Integrative Health
5UH3AT009145-04

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N/A

Sponsor of IND (IDE):

N/A

Tool Revision History

Version Number: 2.1
Version Date: July 6, 2018
Summary of Revisions Made:

- Revised sample size from 202 to 122. The total sample size of n=122 is comprised of n=50 for the MB-BP intervention group; n=50 for the enhanced usual care control group; and n=22 for the exploratory MBSR group. This sample size reflects recruitment during UH3 phase rather than during both the UH2 and UH3 phases.
- Mediation analyses will be performed via meta-analysis of both samples from the UH2 and UH3 phases, for which the participants were assessed using identical methods. This will maximize statistical power for mediation analyses, which require greater power.
- Narrowed primary outcome to one (Multidimensional Assessment of Interoceptive Awareness), in order to minimize issues of multiple statistical testing and maximize statistical power, given the smaller sample size when analyses are restricted to the data collected during the UH3 phase.
- A unique clinicaltrials.gov registration will be created based on the UH3-specific aims, data collection, and analyses.

Version Number: 2.2
Version Date: August 9th, 2018

Summary of Revisions Made: Replaced Dr. Wen-Chih Wu with Dr. Gaurav Choudhary as the clinical cardiologist on the DSMB. This was done because Dr. Wu and Dr. Loucks have published together in the past three year. Dr. Choudhary and Dr. Loucks have not published together.

Version Number: 2.3
Version Date: August 16, 2018
Summary of Revisions Made:

- Addressed comments and requested revisions per OCRA 8/9/18 review. Comments were relayed by Program Director, Merav Sabri, to study PI, Eric Loucks in an email sent on August 10, 2018.
- Revised Appendix B as requested by OCRA. Also removed sub-Appendix A, Conducting Orientation Sessions at the Center for Mindfulness in Medicine, Health Care and Society University of Massachusetts Medical School, as it is not utilized in this study
- Updated phone screener document (Appendix C) to reflect OCRA review comments and updated study protocol.
- Replaced informed consent form (Appendix D) with updated version (v.3.2)

Version Number: 2.4
Version Date: November 14, 2018

Summary of Revisions Made: The modifications made to the study protocol outlined below were largely the result of items brought to the research team's attention during the NCCIH/Westat September 13, 2018 Site Initiation Visit (SIV) and in the related SIV Report sent on October 9, 2018.

- Updated the study team roster to include the co-PI (King); data safety monitoring expert (Britton); and the study clinicians (Wu and Flynn).
- Clarified the role UMass Medical School will play in conducting the fMRI imaging study and explicitly stated that the details of said study will be documented separately.
- Removed the MBSR exploratory arm. (Refer to Nov. 6, 2018 PI email to NCCIH PO for rationale. NCCIH provided written approval in Nov. 12, 2018 email response to PI)
- Revised (clarified) descriptive language around recruitment; screening; inclusion criteria; blinding; randomization procedures; intervention timing, duration, and content; assessment windows; and data management to more accurately reflect the plan for UH3 study procedures.
- Updated the full list of measures for UH3, which included the removal of: actigraphy devices, Mindful Skill Acquisition scale, dietary self-efficacy, and the readiness to change for hypertenstive risk factors questionnaire. Additionally, the following measures were added: the PROMIS Global Health v.1.2 scale, childhood food insecurity questionnaire, alcohol consumption, mindfulness home practice questions, the Connor-Davidson Resilience scale, the Self-efficacy for chronic disease management questionnaire, and 6-month semi-structured exit interview questions.
- Revised Section 7 (Safety Assessments) to reflect the new Data safety and monitoring plan (DSMP) put forth for UH3.
- Clarified language around the estimated enrollment and analyzable sample size for the fMRI Study.
- Corrected clerical and grammatical errors and cleaned up the language to be more concise and clear.

Version Number: 2.5

Version Date: December 11, 2018

Summary of Revisions Made: Addressed the comments and requested clarifications sent to study PI (Loucks) by NCCIH Program Director (M. Sabri) on December 6, 2018 at 6:18 PM EST. The specific revisions include:

- Adding clarifying language on study randomization and cohort size to section 6.2.4 (Randomization and Intervention Allocation).
- Expounding upon circumstances that might possibly lead to Investigator-initiated withdrawals, which are discussed in section 7.3.3. of the Safety Assessment section of the protocol.

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PARTICIPATING STUDY SITES

There is one study site, Brown University, carrying out the Mindfulness-Based Blood Pressure Reduction (MB-BP) study protocol outlined in this document. The University of Massachusetts Medical School is conducting the fMRI Imaging study that will recruit and scan a subset of MB-BP study participants (see separate fMRI study protocol and related MOP for full detail).

PROTOCOL SUMMARY

Study Title

Mindfulness Based Blood Pressure Reduction: Stage 2a Randomized Controlled Trial

Objectives

1. ***Impacts of MB-BP on Primary Self-Regulation Targets:*** Identify the impacts of MB-BP *vs*. enhanced usual care on the primary self-regulation target, specifically an assay of self-related processes (MAIA), described in Table 1. We hypothesize that MB-BP will significantly improve the MAIA in directions of better self-regulation, compared to control.
    a. Secondary analyses will evaluate impacts on secondary self-regulation targets including an assay of emotion regulation (DERS), and cognitive processes (SART), described in Table 1.
    b. Exploratory analyses will evaluate engagement of MB-BP *vs*. enhanced usual care with triangulated self-regulation target assays described in **Table 1** such as emotion regulation and stress (Pittsburgh Stress Battery, Perceived Stress Scale), self-related processes (Heart Beat Detection Task, Interoceptive Awareness fMRI Task), and cognitive processes (Mindful Attention Awareness Scale). Measures such as the neuroimaging Interoceptive Awareness fMRI Task will replicate assays in the MINDFUL-PC study.
2. ***Self-Regulation Targets as Mediators of MB-BP Effect on Medical Regimen Adherence and Health Behavior Change:*** Evaluate the degree to which the engagement of MB-BP with self-regulation targets translates into improved prehypertension/hypertension medical regimen adherence, specifically for the Dietary Approaches to Stop Hypertension (DASH)-consistent diet. We hypothesize that MB-BP will increase the DASH diet score compared to control, in participants with low DASH diet adherence at baseline (DASH diet score <5.5), and that the self-regulation primary outcome in Aim 1 (i.e. MAIA) is a significant mediator.
3. ***Further develop an MB-BP therapist manual and training program, including procedures for training, supervising, and evaluating therapists.*** The PI will implement training he receives from the University of Bangor in the United Kingdom in May 2018 to implement the Mindfulness-Based Interventions Teacher Assessment Criteria (MBI-TAC) for MB-BP instructors, which is the most respected quantitative and qualitative tool developed to provide feedback for enhancing MBI teacher effectiveness, and establishing teacher certification.[1-3]

Design and Outcomes

During the UH3 phase, we will perform a Stage 2a[4] two-arm RCT of MB-BP *vs*. enhanced usual care control, enrolling 50 individuals aged 18 years of age and older per group. This is a pragmatic control group designed to inform physicians if MB-BP would be of service to refer patients, compared to enhanced usual care they could provide patients in well-resourced settings. This control group was decided upon through recommendations by the Research Coordinating Center at Columbia University, the Data Safety Monitoring Board, and several collaborating cardiologists and family physician clinician-researchers. Enhanced usual care involves every participant being provided with a validated home blood pressure monitor (Omron, Model PB786N), which has evidence in and of itself to potentially lower blood pressure,[5,6] and is beyond usual care at this time. All participants who have Stage 2 hypertension (blood pressure >140/90 mmHg) will be offered to have their physicians notified, if not already being overseen for uncontrolled hypertension. For participants with uncontrolled hypertension who do not have a physician, we will work with participants to provide access within constraints of their health insurance. Enhanced usual care group participants receive an educational brochure from the American Heart Association entitled “Understanding and Controlling Your High Blood Pressure Brochure” (product code 50-1731).

Blinding

All study staff will be blinded to the participant treatment allocation with the exception of the instructor, individual who performs the randomization, and staff member coordinating participants within each course. All staff performing participant assessments will be blinded to the participant treatment allocation to promote equipoise. Data analyses will be performed by a statistician blinded to treatment allocation type. The data manager will be able to break blinding if needed (e.g. for Data and Safety Monitoring Board).

Intervention Allocation

Stratified randomization will be used, as simple randomization can fail if it creates groups unbalanced for critical features known to affect outcomes.[7,8] Stratified randomization can reduce both types I and II error, improve trial efficiency, and facilitate subgroup and interim analyses.[7] Randomization will be done using an online computer software program known as Research Randomizer (Version 4.0).[9] The randomization process will occur after each new round of enrollment. Study enrollment will continue until target enrollment goals are reached (i.e., n=50 for MBBP intervention group, n=50 for enhanced usual care control group).

Interventions and Duration

Two-arm RCT comparing MB-BP vs. enhanced usual care. Follow-up assessments will take place within pre-defined assessment windows occurring around 10 weeks, 6 months, and 1 year post- intervention commencement. For participants on waitlist enhanced usual care, they will be offered MB-BP after the 6-month follow-up with no additional assessments unless they would like the assessments for follow-up information on changes in their health. Participants in the intervention group will be asked to come back at the 1-year follow up window for an abbreviated follow up assessment. Thus the total length of involvement for study participants will be up to one year from the time of enrollment to the time of the final research assessment. The study intervention lasts 9 weeks, may be nonconsecutive weeks in the event of a holiday or instructor availability, and takes place in the first three months for individuals in the intervention arm.

Sample Size and Population

We anticipate needing to recruit and enroll a total of 100 eligible individuals during Phase 3. This will consist of 50 individuals per group for both the MB-BP intervention arm and the enhanced usual care arm. (see Figure 1 below for detail).

For more detailed discussion of group allocation, stratification factors, and how it influences study population, please refer to Section 6.2.4.

Inclusion/exclusion criteria:

Inclusion Criterion: Elevated blood pressure defined as ≥120 mmHg systolic or ≥80 mmHg diastolic pressure;[10] able to speak, read, and write in English; all adults (≥18 years of age), genders and racial/ethnic groups are eligible to be included.

Exclusion Criteria: Exclusion criteria follow standard guidelines and recommendations:[11] (a) current regular meditation practice (>once/week); (b) serious medical illness precluding regular class attendance; (c) current substance abuse, suicidal ideation or eating disorder, (d) history of bipolar or psychotic disorders or self-injurious behaviors. These participants are excluded

because they may disrupt group participation, require additional or specialized treatment, or are already participating in practices similar to the intervention.

1. STUDY OBJECTIVES

1.1 Primary Objective

1. ***Impacts of MB-BP on Primary Self-Regulation Targets:*** Identify the impacts of MB-BP *vs*. enhanced usual care on the primary self-regulation target, specifically an assay of self-related processes (MAIA) described in Table 1. We hypothesize that MB-BP will significantly improve the MAIA in directions of better self-regulation, compared to control.
    a. Secondary analyses will evaluate impacts on secondary self-regulation targets including an assay of emotion regulation (DERS), and cognitive processes (SART), described in Table 1.
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2. ***Self-Regulation Targets as Mediators of MB-BP Effect on Medical Regimen Adherence and Health Behavior Change:*** Evaluate the degree to which the engagement of MB-BP with self-regulation targets translates into improved prehypertension/hypertension medical regimen adherence, specifically for the Dietary Approaches to Stop Hypertension (DASH)-consistent diet. We hypothesize that MB-BP will increase the DASH diet score compared to control, in participants with low DASH diet adherence at baseline (DASH diet score <5.5), and that the self-regulation primary outcomes in Aim 1 are significant mediators.
3. ***Further develop an MB-BP therapist manual and training program, including procedures for training, supervising, and evaluating therapists.*** The PI will implement training he receives from the University of Bangor in the United Kingdom in May 2018 to implement the Mindfulness-Based Interventions Teacher Assessment Criteria (MBI-TAC) for MB-BP instructors, which is the most respected quantitative and qualitative tool developed to provide feedback for enhancing MBI teacher effectiveness, and establishing teacher certification.[1-3]

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The World Health Organization reported that suboptimal blood pressure (BP) is responsible for more than half of cardiovascular disease mortality world-wide. Furthermore, greater than half of those with hypertension have uncontrolled BP.[12] *A 2009 Institute of Medicine report recommended prioritizing research to "Compare the effectiveness of mindfulness-based interventions (e.g. yoga, meditation, deep breathing training) and usual care in treating… cardiovascular risk factors."* [13] Evidence-based mindfulness interventions, including Mindfulness-Based Stress Reduction, may have some effects on blood pressure, where a recent meta-analysis and systematic review of 4 randomized controlled trials demonstrated

significant effects, but evidence of heterogeneity in effect sizes.[14] The methodologically highest quality studies had the smallest effect sizes (range 0-5 mmHg).[14] Mindfulness-Based Stress Reduction (MBSR) has been customized to a number of disease processes, such as Mindfulness-Based Cognitive Therapy for patients with recurrent depression, and Mindfulness-Based Relapse Prevention for patients with substance use addictions.[15-17] Effect sizes may be increased by customizing mindfulness interventions to diseases of interest. The same may be true for hypertension, *however mindfulness interventions customized for prehypertensive/hypertensive patients have never been investigated. Until methodologically rigorous studies to evaluate customized interventions for hypertension are performed, we will not know if the observed preliminary effects of general mindfulness interventions on blood pressure reduction could be much more effective with a tailored approach.*

The development of effective interventions that enhance the capacity for self-regulation among people with chronic health conditions is a major public health challenge in the United States and worldwide. The process of healthcare system transformation that is underway focuses on moving accountability for healthcare costs to healthcare systems.[18] Meanwhile, in order to survive, healthcare systems must rapidly learn to deliver interventions that can enhance their patients' capacity to self-manage these deadly and costly chronic health conditions.[19] While access to care[20] and health education[21] are essential, a person's capacity for self-regulation is often the primary limiting factor in their ability to adhere to their medical regimen, collaborate on illness self-management, and reduce health risk behaviors.[22-25] Self-regulation refers to the process of managing cognitive, emotional, and self-relevant resources to align mental states and behavior with goals.[26-28] Changing risk behaviors that influence hypertension risk, such as physical inactivity, diet, excessive alcohol use, and poor medication adherence, requires skills for self-regulation that are broadly applicable within multiple environments. A research collaboration that could test methods for engaging self-regulation mechanisms, identify specific target tests, and rapidly integrate these into an empirically-optimized clinical interventions that are ready for implementation and rapid dissemination within health care settings for patients with chronic illness would make a substantial impact on chronic illness management and the entire healthcare system. Mindfulness-Based Interventions (MBIs) have already begun to offer feasible basic building blocks for the rapid integration of an empirically-optimized, trans-diagnostic, self-regulation toolkit into healthcare across multiple contexts and age groups.

Mindfulness meditation, a form of training that involves maintaining a non-judgmental form of attention to immediate experience,[29] has been employed in both clinical and non-clinical settings to facilitate self-regulation and behavior change.[30-34] Mindfulness-Based Interventions (MBIs),[35] sometimes referred to as "3rd Wave Behavioral Therapies,"[36] have become widely used in both clinical and non-clinical settings, including prisons,[37,38] the military,[39-41] and both K-12[42-45] and higher education,[46] and are emerging as a wide-spread, potentially cost-saving,[47] comprehensive methods for enhancing self-regulation in multiple medical contexts. *While MBIs efficacy has been demonstrated for several conditions related to self-regulation,[48-50] the field lacks consensus about the mechanisms through which these interventions engage self-regulatory processes and impact of MBIs on medical regimen adherence and health behavior changes. Without this knowledge, a plethora of MBIs are being developed without systematically building on discoveries of which components of the interventions have the most impact on specific health behaviors and outcomes.* As a result, the interventions are not as rigorous in their design, which may limit their efficacy and account for some of the mixed results found in the literature.

Self-regulation requires both *initiating* behavior change and *maintaining* behavior change,[51,52] implying corrective adjustments originating within a person and taking place as needed in order

to maintain and sustain the intended goal. Self-regulatory failure is primarily determined by deficits in (or depletion of) self-regulatory strength,[53] highlighting the need for interventions that strengthen self-regulation capacity. Current behavioral models lack a full integration of tools for strengthening self-regulation towards both initiation and maintenance of behavior change.[51,52] Strategies focusing on extrinsic rewards or behavioral economics can help change behavior, but intrinsic motivation is ultimately essential to self-regulation.[54] Behavioral and psychological therapies can provide emotional regulation strategies and some even include motivational components;[55,56] however, they generally lack tools to strengthen core cognitive resources, such as attention and inhibitory control, which are necessary to support maintenance of behavior change. *In contrast, MBIs uniquely integrate training in the emotional, motivational, and cognitive aspects of self-regulation within one therapeutic intervention.* By frequently returning attention to the present moment with a specific orientation to experience (curious, open-minded, and accepting), mindfulness practice strengthens the capacity for frequent daily corrective adjustments needed to stay on track with intended goals. Studying how common self-regulation targets influence, and are influenced by, various components of MBIs provides a unique opportunity to develop an easy-to-disseminate, integrated therapeutic intervention optimized with the most potent components for enhancing self-regulation within the context of medical regimen adherence and the initiation and maintenance of health behaviors.

Following recent proposals on the mechanisms of action of mindfulness by our group[30,57] and others,[58-62] *three broad self-regulation domains of mindfulness can be identified:*

(A) Cognitive processes, including attention (i.e. orienting, alerting,[63,64] vigilance,[65] and conversely sleepiness, cognitive fatigue, attentional lapses, and mind-wandering[66]); executive function, conflict monitoring,[67,68] impulsivity and inhibitory control,[69,70] and metacognitive awareness.[71-73] Many studies indicate that meditation training, such as MBIs, engage these cognitive processes.[74-87]

(B) Emotion regulation, which is the capacity to alter the magnitude or duration of an emotional response.[88] Poor emotion regulation impairs the capacity for self-regulation behaviors that support health behaviors[89-92], including medical regimen adherence.[93] MBIs favorably engage measures of emotion regulation such as amygdala activation,[79,94-97] sympathetic hyperarousal,[98-103] and emotional responses to stressful situations,[102,104-111] although opposite findings have also been reported[112-114] which leads to the question (to be addressed by this collaborative) of which conditions affect target engagement.

(C) Self-related processes, including: *(i) self-efficacy* – the belief in one's capabilities to execute the courses of action required to manage prospective situations (such as changing and maintaining a medical regimen),[115,116] which is a central aspect of self-regulation and changes in health behavior;[117,118] *(ii) self-compassion* – the capacity to extend compassion to oneself in instances of perceived inadequacy or failure rather than engaging in either self-destructive behaviors (self-judgment, isolation, rumination) or in permissive, risky behaviors:[119-121] self-compassion has been found to promote health behaviors such as adhering to diets,[122] smoking cessation,[123] physical activity,[124] and seeking medical treatment when needed;[125] *(iii) self-related rumination or mind-wandering* – which may be beneficial in some cases[126-128] but detrimental in others[129-133] and is a central topic in MBI research, by our group[57,134] and others;[135] and *(iv) interoceptive awareness* – the awareness of internal manifestations of emotions and feelings, considered fundamental to the 'experiencing self',[136-141] a particular form of awareness which can be enhanced by the paying of purposeful, nonjudgmental attention ('mindfulness') to inner body sensations,[32,33,142] which is also of major interest in MBI research.[30,62,135,143-160]

Consequently, we propose to conduct a Stage 2a behavioral intervention study to evaluate whether MBSR customized to pre-hypertensive and hypertensive patients has the potential to provide clinically relevant reductions in BP.

2.2 Study Rationale

The MB-BP Study aims to customize the standardized MBSR[161-164] intervention to adult participants with prehypertension or uncontrolled hypertension. Similar to MBSR, the MB-BP intervention consists of eight 2.5-hour weekly group sessions (plus a 2.5-hour orientation session) and an 8-hour one-day session, led by a certified MBSR instructor with extensive cardiovascular disease and hypertension expertise.[165-178] MB-BP builds a foundation of mindfulness skills (e.g. meditation, self-awareness, etc.) through the MBSR curriculum. MB-BP then directs attention towards hypertension risk factors. The unique areas of MB-BP are education on hypertension risk factors, hypertension health effects, and specific mindfulness modules focused on awareness of diet, physical activity, medication adherence, weight loss, and alcohol consumption and their effects on well-being. A curriculum guide has been created based on the standardized MBSR manual (**Appendix A)**, and was further developed through the approaches described above, and sequentially revised based on participant feedback and preliminary findings.[163,164] MB-BP participants learn a range of mindfulness skills including body scan exercises, meditation and yoga. Homework consists of practicing skills for ≥45 min/day, 6 days/week.

3. STUDY DESIGN

We will perform a Stage 2a[4] two-arm RCT of MB-BP *vs*. enhanced usual care control. This is a pragmatic control group designed to inform physicians in well-resourced settings if MB-BP would be of service to refer patients to as compared to enhanced usual care patients. The study is intended to evaluate the impacts of MB-BP on the primary self-regulation outcome of interoceptive awareness (i.e. MAIA) as compared to an enhanced usual care group. Secondary self-regulation outcomes are described in the Objectives section outlined previously. This study also aims to evaluate the degree to which the engagement of MB-BP with self-regulation targets translates into improved prehypertension/hypertension medical regimen adherence, specifically for the Dietary Approaches to Stop Hypertension (DASH)-consistent diet.

The enhanced usual care control group was decided upon through recommendations by the Research Coordinating Center at Columbia University, the Data Safety Monitoring Board, and several collaborating cardiologists and family physician clinician-researchers. Enhanced usual care involves every participant being provided with a validated home blood pressure monitor (Omron, Model PB786N),[179] which has evidence in and of itself to potentially lower blood pressure, and is beyond usual care at this time.[6,180] All participants who have Stage 2 hypertension (blood pressure >140/90 mmHg) will be offered to have their physicians notified, if not already being overseen for uncontrolled hypertension. For participants with uncontrolled hypertension who do not have a physician, we will work with participants to provide access within constraints of their health insurance. Enhanced usual care group participants receive an educational brochure from the American Heart Association entitled “Understanding and Controlling Your High Blood Pressure Brochure” (product code 50-1731).

All research assessments will take place in the Brown University Mindfulness and Cardiovascular Health Lab in Providence, RI. The MB-BP intervention classes will be offered in both a University and community-based setting.

Baseline assessments for all enrolled participants will take place within four weeks of the start of the intervention. Follow-up assessments will take place during the 10 week, 6 month, and 1 year assessment windows, which are defined as: (a) “10 week” follow up assessments are to occur at least one day after and up to five weeks after the end of the intervention (i.e. the Week 8 class). Staff will prioritize completing the assessments within the first three weeks of the assessment window, but will allow for participants to complete up to five weeks after. (b) The “6-month” follow up assessments will be scheduled to occur six months from the orientation class date plus or minus 2.5 weeks. This allows for a five-week data collection period with prioritization given to the three-week window surrounding the official six-month date. (c) The “1 year” follow up assessments are to be completed with the intervention group participants only and will occur one year plus or minus a month after the start of the intervention (i.e., orientation date).

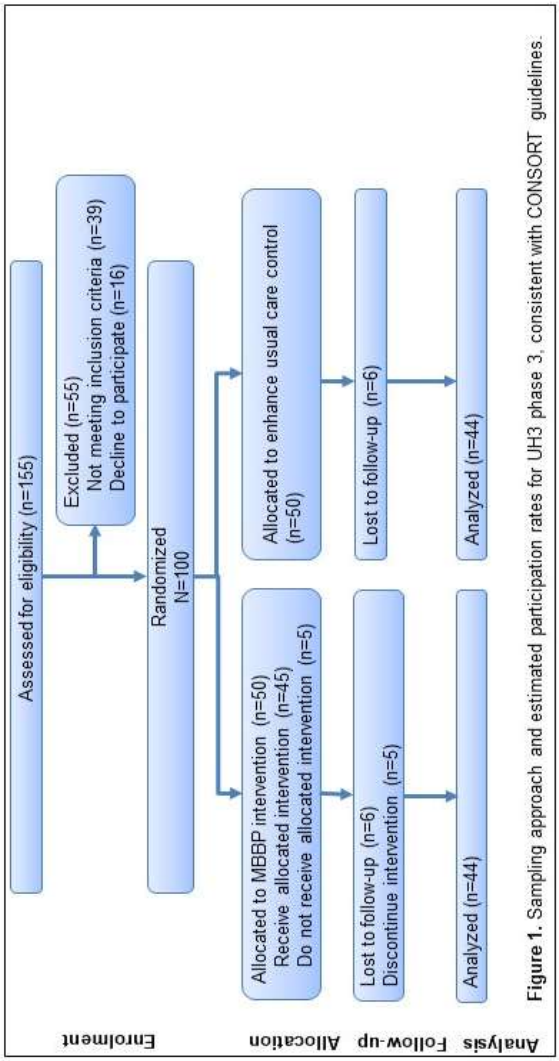

Figure 1. Sampling approach and estimated participation rates for UH3 phase 3, consistent with CONSORT guidelines.

If a participant is unable to complete an assessment within the defined data collection window, but still wishes to participate, we will allow for the participant to complete an online home survey and/or in person follow up assessment beyond the parameters defined above.

Participants who were randomized to the waitlist enhanced usual care group will be offered MB-BP after the 6 month follow-up assessment is complete with no additional assessments unless they would like the final one year assessment for follow-up information on changes in their health. Thus the total length of involvement for study participants will be up to one year from the time of enrollment to the time of the final research assessment. The study intervention lasts 9 weeks and takes place in the first two months for individuals in the intervention arm. The intervention will be offered several times a year over the course of the total study duration.

Prehypertension/Hypertension Medical Regimen Adherence Outcomes Assessment Methods:

Primary Prehypertension/Hypertension Medical Regimen Adherence Outcome: Dietary Approaches to Stop Hypertension (DASH) eating pattern score,[181] measured via 80-item Willet food frequency questionnaire,[182] assessing adherence to American Heart Association/American College of Cardiology (AHA/ACC) clinical practice hypertension guidelines DASH eating pattern score (range 0-8).[10,181,183]

Secondary outcomes of medical regimen adherence include the following: *(1) Alcohol consumption:* Amount and frequency of alcohol consumption, will be assessed via self-report utilizing standard questions from the Behavioral Risk Factor Surveillance Survey.[184] AHA/ACC hypertension clinical practice guideline cut-point of healthy alcohol intake is ≤ 2 drinks (e.g. 24

oz. beer, 10 oz. wine, or 3 oz. 80-proof whiskey) per day in men and ≤1 drink per day in women.[10] *(2) Electronically-Measured Antihypertensive Medication Adherence:* measured continuously using electronic medication bottle caps (eCAPS, Ottawa, Canada)[185] *(3) Body Mass Index:* height and weight directly assessed using standard epidemiologic methods, with change evaluated in participants considered overweight or obese (BMI≥25 kg/m^2).[186] *(4) Physical activity:* measured using the International Physical Activity Questionnaire which has undergone substantial validity and reliability testing.[187-189] Adherence to Joint National Commission-7 (JNC-7) guidelines is 30 min aerobic physical activity ≥4 days per week.[183]

Please see Section 6.2.4 for randomization, blinding and stratification methods.

Please see **Figure 1** for study groups including sample sizes. Please note that sample size recruited for the UH3 phase will be 50 participants per group for MB-BP and enhanced usual care control.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Elevated blood pressure or hypertension defined as ≥120 mmHg systolic or ≥80 mmHg diastolic pressure.[10] Able to speak, read, and write in English. All adults (≥18 years of age), genders and racial/ethnic groups are eligible to be included.

4.2 Exclusion Criteria

Exclusion criteria follow standard guidelines and recommendations:[11] (a) current regular mindfulness meditation practice (>once/week); (b) serious medical illness or cognitive condition (e.g., dementia) precluding regular class attendance and/or participation; (c) current substance abuse, suicidal ideation or eating disorder, (d) history of bipolar or psychotic disorders or self-injurious behaviors. These participants are excluded because they may disrupt group participation, require additional or specialized treatment, or are already participating in practices similar to the intervention. Additionally, we will be asking participants randomized to the control group to restrain from engaging in any type of formal mindfulness practice more than weekly during the first six months of study involvement so as to not introduce confounding variables. Individuals will be made aware of this requirement at the time of informed consent (first in-person screening). Anyone who is unwilling to follow the treatement requirement would be ineligible for the study.

4.3 Study Enrollment Procedures

Participants will be recruited in part through cardiology and family practices via established relationships with physicians in Rhode Island and Massachusetts. Graduates from the MP-BP program have proven effective at recruiting their contacts. Furthermore, advertisements will be posted throughout Rhode Island and southern Massachusetts, and distributed via social media, inviting participants interested in lowering their blood pressure to enroll. Additionally, we will partner with local providers to recruit hypertensive patients through methods such as direct mailings and targeted recruitment at the Rhode Island Hospital Emergency Department.

Participants are randomly assigned a participant identifier at the time of screening. The key to participant name and identifier is kept in a secure location separate from the research data. The outcome of every screener completed is recorded in a password protected tracking system and reason for ineligibility is noted. Circumstances surrounding situations where eligible participants decline participation and cases where participants enroll but later withdraw are also documented in a tracking system.

Informed consent is collected at the time of the first in-person screener. Individuals wishing to enroll in the study are provided two copies of the written informed consent form which has been approved by the Brown University Institutional Review Board (IRB). In addition to allowing the participant time to read over the consent form, trained research staff review the important points of consent with each participant. The informed consent process is documented. A signed copy of the consent is kept on file in a secure location in the research lab separate from study data and a copy is offered to the participant to keep with his/her personal records. Due to the nature and delivery of the intervention, all participants must be able to read and write in English and be able to provide informed consent for their participation.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

MB-BP Intervention Description: This study proposes to customize MBSR to participants with prehypertension/hypertension creating an intervention called Mindfulness Based Blood Pressure Reduction Study (MB-BP). Specifically, MB-BP is based on the standardized MBSR intervention described elsewhere,[161-164] and will consist of eight 2.5-hour weekly group sessions, a 2.5 hour orientation, and an 8-hour one-day session. MB-BP will be performed by qualified or certified MBSR instructors[190] with formal training in cardiovascular health (e.g. dietician, physician assistant, health and wellness coach, and those with an Associate's or Bachelor's degree in relevant health sciences), and further certification in MB-BP. MB-BP instructor training involves: (1) An initial 40 hour in-person or online videoconference training where the unique elements of MB-BP are introduced. (2) Two half-day in-person training retreats where MB-BP-specific teaching modules are practiced in peer groups, supervised by the senior MB-BP trainer, with peer and trainer feedback. (3) Studying specific evidence-based articles on hypertension etiology, treatment and prevention, as well as articles synthesizing evidence of mindfulness on hypertension and hypertension risk factors. [10,183,191-193] A written exam evaluates knowledge in this area, for which instructors-in-training need to pass. (4) Supervised teaching of MB-BP in non-study participants is done using the Mindfulness-Based Intervention Teacher Assessment Criteria (MBI-TAC), [1,2,194] and an annotated MB-BP Curriculum Guide until adequate quality is established within predefined criteria.

The unique areas of MB-BP are education on hypertension risk factors, hypertension health effects, and specific mindfulness modules focused on awareness of diet, physical activity, medication adherence, alcohol consumption, stress, and social support for behavior change. A Curriculum Guide has been created based on the standardized MBSR manual developed at UMass Medical School (**Appendix B**).[163,164] MB-BP sessions contain instruction and practice in mindfulness meditation, and conversations about stress and coping. Students learn a range of mindfulness skills including body scan exercises, meditation and yoga. Homework consists of

practicing skills for ≥45 min/day, 6 days/week. All MB-BP classes are to be held in either University or community-based locations in a comfortable, accessible environment where privacy is able to be maintained.

MB-BP builds a foundation of mindfulness skills (e.g. meditation, self-awareness, etc.) through the MBSR curriculum. MB-BP then directs attention towards hypertension risk factors. Early in the MB-BP, the importance of hypertension for health and mortality is described, along with hypertension risk factors. Participants will have their blood pressure and hypertension risk factors assessed at baseline, and be provided with this information during the first in-person MB-BP session. This phase aims to engage participants' interest in hypertension risk factors, and increase motivation for behavior change. MB-BP encourages participants to explore personal readiness for change in the different hypertension risk factors, and explore utilizing mindfulness practices to engage with those risk factors that they choose to. Each week, focus is provided on different hypertension risk factors. However, common themes exist across all hypertension risk factors including (1) awareness of thoughts, emotions and physical sensations particularly surrounding hypertension risk factors such as overconsumption of palatable foods, sedentary activities, alcohol consumption, medication adherence; (2) craving, particularly for hypertension risk factors such as overconsumption of palatable foods, sedentary activities, and alcohol consumption; (3) the impact of bringing mindfulness to every moment, particularly in relation to hypertension risk factors. For example, when consuming highly palatable food, bringing awareness to the emotions, thoughts and physical sensations prior to eating, during eating, and in the time afterwards. Participants are trained to bring non-judgmental attention to the often short-term pleasure of overconsumption of foods, sedentary activities, heavy alcohol consumption, or not taking medications, and bring non-judgmental attention to the longer term suffering associations with these activities. Through this process, participants are encouraged to reflect on if behavioral choices provide more benefit or harm to their well-being, and to choose the behaviors that bring benefit. (4) Self-care: as awareness of thoughts, emotions and physical sensations increases, and self-regulation will likely increases as a result of the meditation practices, the curriculum will emphasize to participants that it is common for people to start caring for themselves more. It is a way of better knowing ourselves, and through knowing ourselves in in each moment, we often want to care for ourselves in each moment. This may mean taking medication that will help our health, or being more physical active, eating more healthily, or consuming more moderate amounts of alcohol.

5.2 Handling of Study Interventions

Please see Appendices A and B for the MBSR and MB-BP curriculum guides.

5.3 Concomitant Interventions

Please see inclusion/exclusion criteria in Sections 4.1 and 4.2.

5.4 Adherence Assessment

Adherence to the prescribed MB-BP practices will be monitored through class attendance, practice logs and weekly health goals. Adherence data will be collected weekly during the course of the intervention. Dr. Schuman-Olivier is testing more

technologically enhanced forms of meditation logs (e.g. accelerometer-based ecological momentary assessment and actigraphy score; NCT01314378), and found large proportions of participants had difficulty using the device properly (e.g. failing to stop meditation timers), which hampered data quality (*paper in progress*). We discussed this issue with leading meditation researchers, and meditation logs remain their recommended method at this time. However, innovative approaches are being explored by Dr. Lazar, including smartphone apps linked to audio homework files, with timers linked to data exports. These technologies are not yet ready for use, but we will incorporate technological advances for homework monitoring once demonstrated to be effective. Data analyses will evaluate effect modification by adherence to the MB-BP practices.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Variables Measured	Assessment Times			
	Baseline	10 weeks	6 months	1 year*
Demographics	X			
Family history of hypertension	X			
Childhood Socioeconomic Status	X			
Adverse Childhood Experiences	X			
Depressive Symptomatology	X	X	X	
Anxiety	X	X	X	
Medication Use	X	X	X	X
Anti-Hypertensive Medication Adherence	X	X	X	
Blood pressure	X	X	X	X
Anthropometry	X	X	X	X
Physical Activity	X	X	X	
Diet	X	X	X	X
Alcohol consumption	X	X	X	X
Cigarette Smoking	X	X	X	
Sleep Duration	X	X	X	X
Mindfulness	X	X	X	
Mindfulness home practice	X	X	X	X
Emotional Eating	X	X	X	
Self-Compassion	X	X	X	
Perceived Stress	X	X	X	
Emotional Regulation	X	X	X	X
Interoception	X	X	X	X
Heartbeat Detection	X	X	X	
Decentering	X	X	X	
Attention Control	X	X	X	
Craving for Hypertensive Risk Factors	X	X	X	
Social Integration	X	X	X	
Loneliness	X	X	X	
PROMIS Global Health	X	X	X	
Self-Control	X	X	X	
Resilience	X	X	X	
Self-efficacy for managing chronic disease	X	X	X	
Stress Reactivity	X	X	X	
Delay Discounting	X	X	X	
Semi-structured exit interviews at 6 months			X	

**1-year assessments consist of a subset of the other two follow ups and will be completed only with intervention group as controls are offered course post 6-month follow-up*

6.2 Description of Evaluations

6.2.1 Screening Evaluation and Consenting Procedure

Please see **Appendices C and D** for the consenting process prior to the phone screening, and prior to the in-person screening.

Final screening evaluations will occur at least one week prior to baseline assessments. Baseline assessments will occur within 4 weeks of intervention initiation.

Phone-Based Screening: For people who indicate interest in the study, this screening will take place by phone using trained research assistants to assess the exclusion criteria described above, with the exception of blood pressure which will be assessed in-person

In-Person Screening: If participants remain eligible after the phone-based screening, they will attend an in-person screening for blood pressure and medication assessment. If mean blood pressure is elevated (≥120 mmHg systolic and/or ≥80 mmHg diastolic pressure), participants will be invited to return for a second blood pressure reading. At that time, if the mean blood pressure across both assessment times is ≥120 mmHg systolic or ≥80 mmHg diastolic pressure, they will be invited to participate in the study.

6.2.2 Enrollment

The enrollment date is the day that the individual has met all the screening criteria, signs the informed consent form, and confirms agreement to participate in the study.

6.2.3 Baseline Assessments

(1) Demographics: age, race/ethnicity, socioeconomic status (education, employment), and household structure.
(2) Family History of Hypertension (FH): Assesses biological parents' history of having hypertension, based on questions from New England Family Study LEAP Project.
(3) Childhood socioecononomic status: retrospective reporting of parents' education, based on standardized questionnaires used in the Atherosclerosis Risk in Communities (ARIC) study.
(4) Adverse Childhood Experiences: Measured using the standardized Childhood Trauma Questionnaire (CTQ), Childhood food insecurity questionnaire, and the Childhood Experiences of Care and Abuse Inventory neglect subscale. [184,195-200]
(5) Depressive symptomatology: Assessed using Center for Epidemiologic Studies Depression Scale Revised (CESD-R). The CESD survey has been used extensively in the epidemiologic literature to assess depressive symptomatology.[201] The scale was updated to the CESD-R by Van Dam *et al*., which allows diagnosable criteria similar to Diagnostic and Statistical Manual (DSM) of Mental Disorders.[202]
(6) Anxiety: Assessed using the validated Beck Anxiety Inventory.[203-209]
(7) Medication use: Assessed directly from participants' medication bottles and self-report using standardized forms, including medication name, dose, frequency of use, and reason of use.
(8) Antihypertensive medication adherence: measured continuously using electronic medication bottle caps (eCAPS, Ottawa, Canada).[185]

(9) *Systolic and diastolic blood pressure:* Clinical blood pressure will be measured using a calibrated Omron HEM-705CPN following American Heart Association and Joint National Committee (JNC) guidelines.[183,210,211] Additionally, participants will be asked to complete three at home blood pressure readings using a validated home blood pressure monitor (Omron, Model PB786N) provided at baseline.

(10) *Anthropometry:* height and weight directly assessed using standard epidemiologic methods.[186]

(11) *Physical activity:* The International Physical Activity Questionnaire which has undergone substantial validity and reliability testing.[187-189] Adherence to Joint National Commission-7 (JNC-7) guidelines is 30 min aerobic physical activity ≥4 days per week.[183]

(12) *Diet*: assessed utilizing the validated Food Frequency that allows for calculation of hypertension-related dietary factors, including salt intake, alcohol consumption, total caloric consumption, fruit and vegetable consumption, and Dietary Approaches to Stop Hypertension (DASH) eating pattern score.[182]

(13) *Alcohol consumption:* additional self-report standardized questions assessing current alcohol consumption taken from the Behavioral Risk Factor Surveillance Survey (BRFSS).[212]

(14) *Cigarette smoking:* current smoking assessed using self-report standardized questions from the New England Family Study.

(15) *Sleep duration:* Sleep duration is assessed using a single question on sleep duration from the validated Pittsburgh Sleep Quality Index (PSQI).[213-215]

(16) *Mindfulness:* Assessed using the validated Five Facet Mindfulness Questionnaire.[216]

(17) *Mindfulness Home Practice:* questions capturing individuals at home mindfulness practice pre- and post- intervention are administered at each of the time points.

(18) *Emotional eating:* measured using the Three Factor Eating Questionnaire Revised 21-item (TFEQ-R21).[217,218]

(19) *Self-compassion:* Assessed using the validated Self-Compassion Scale Short Form (SCS-SF).[121]

(20) *Perceived stress:* Assessed using the validated 14-item Perceived Stress Scale.[219,220]

(21) *Emotion regulation:* Measured using the validated Difficulties in Emotion Regulation Scale.[221]

(22) *Interoception:* Assessed directly using the Heartbeat Detection Task and in secondary self-report using the validated Multidimensional Assessment of Interoceptive Awareness (MAIA).[222-225]

(23) *Decentering:* Assessed using the validated Experiences Questionnaire.[226,227]

(24) *Attention control:* Assessed using the Sustained Attention to Response Task (SART). The SART is a validated computerized test of sustained attention, response inhibition (executive function) and self-regulation.[228-230 231-233]

(25) *Craving:* craving for hypertension risk factors, including palatable foods, alcohol, and sedentary activities will be assessed using the validated Craving Experiences Questionnaire. [234]

(26) *Social integration:* Measured using the validated 12-item Interpersonal Support Evaluation List (ISEL-12) measure of social support.[235]

(27) *Loneliness:* Assessed using the validated R-UCLA Loneliness Scale.[236]

(28) *Global Health:* individual physical, mental and social health are measured using the validated NIH PROMIS Global Health v1.2 scale.[237]

(29) Self-control: assessed using the validated Self-Control Scale short form.[238,239]
(30) Resilience: measured using the validated 10-item Connor-Davidson Resilience Scale (CD-RISC-10).[240]
(31) Self-efficacy for chronic disease management: measured using the 6-item Self-efficacy for Managing Chronic Disease scale (SECD-6).[241]
(32) Stress Reactivity: Assessed using the Pittsburg Stress Battery a standardized protocol of 3 computerized tasks designed to induce a stress response indicated by evaluated cardiovascular (CV) reactivity.[242]
(33) Delayed Discounting: Assessed using the validated 5-Trial Adjusting Delay Discounting Task. [243]
(34) Functional Magnetic Resonance Imaging (fMRI): Participants in the UH3 phase who elect to take part in the fMRI imaging study will undergo an fMRI scanning session for approximately 40 minutes at baseline and 10-week follow-up. Scans will be acquired with a 3T scanner while the subject is in the resting state. Final sample size will be 24 per group (n=48); enrolling up to 60 participants in total to reach target sample size. Participants will undergo a separate informed consent and screening process for the fMRI imaging, so that they can be in the MB-BP study without imaging if they prefer. Refer to the separate fMRI study protocol for details.

6.2.4 Randomization and Intervention Allocation

Randomization will occur following the completion of baseline assessments prior to the initiation of study intervention. Only individuals who complete the baseline assessments and indicate they are available for the upcoming courses will be included in the randomization process.

Stratified randomization will be used, as simple randomization can fail if it creates groups unbalanced for critical features known to affect outcomes.[7,8] Stratified randomization can reduce both types I and II error, improve trial efficiency, and facilitate subgroup and interim analyses.[7] Variables used to create strata include age (≤60 *vs.* >60 years), gender (male *vs.* female), and/or uncontrolled hypertension (≥140 mmHg systolic pressure, or ≥90 mmHg diastolic pressure) *vs*. prehypertension (120 to <140 mmHg systolic pressure, and 80 to <90 mmHg diastolic pressure). Simple random sampling will occur within each of the eight strata, thus allowing for each arm of the study to be more balanced with respect to age, gender, and hypertension category. The total size of each stratum will vary from cohort to cohort. To conduct the randomization, a list of participant IDs and strata characteristics will be provided, and a trained researcher not affiliated with the study will perform the randomization on participants after baseline assessment and final determination of eligibility is complete. Randomization will be done using an online computer software program known as Research Randomizer (Version 4.0).[9] The randomization process will occur after each new round of enrollment (i.e., unique cohort). If the cohort sample size is such that there are not enough participants for balance within the three strata, we will prioritize stratification by two key strata instead of three, specifically by baseline blood pressure status and gender. Furthermore, after randomization within strata, if sample sizes in the entire sample for cohort differ by more than one participant per group, then all imbalanced groups are re-randomized until the entire sample differs by no more than 1 participant per group (e.g. n=8 MB-BP, n=9 enhanced usual care control). Expected cohort sizes, consistent with the

SARP are 15-20 participants. We anticipate needing to run 6 to 7 cohorts to reach the target sample size.

Study enrollment will continue until target enrollment goals are reached (i.e., n=50 for MBBP intervention group and n=50 for enhanced usual care control group).

6.2.5 Blinding

All study staff will be blinded to the participant treatment allocation with the exception of the instructor, individual who performs the randomization, and staff member coordinating participants within each course. All staff performing participant assessments will be blinded to the participant treatment allocation to promote equipoise. Data analyses will be performed by a statistician blinded to treatment allocation type. The data manager will be able to break blinding if needed (e.g. for Data and Safety Monitoring Board). Circumstances for breaking the blind would be a large number of adverse experiences (>10% of enrolled participants reporting AEs rated as severe or life threatening) taking place in one or more study group. In this case, the data safety monitoring board would be notified, and could break the blind to help determine the cause of the adverse experiences.

6.2.6 Follow-up Visits

Follow-up assessments will be scheduled and conducted within the pre-defined assessment windows outlined previously in section 3, study design. Questionnaires and assessments administered at 10 weeks and 6-months follow-up are identical to those administered at the first in-person screening assessment and at baseline, with the exception that questionnaires for which the answers should not change or be informative (age, race/ethnicity, education, adverse childhood experiences, family history of hypertension) are not given at follow-ups. In addition, adverse events are monitored and documented at each of the follow-up periods as well as throughout the duration of an individual's study involvement according to the data safety monitoring protocol put forth in this grant. Participants are also asked a set of semi-structured questions at the end of their six month follow up that inquire about their experience as either a control group member or intervention group participant.

6.2.7 Completion/Final Evaluation

For control group participants, the 6-month evaluation is the final visit. Upon completion of this assessment, they will be eligible to participate in the MB-BP training. Individuals in the intervention group will be assessed at 1 year follow up with a subset of measures (see Table 6.1 Schedule of Evaluation) in order to assess long term effects of the intervention.

7. SAFETY ASSESSMENTS

7.1 Expected Risks and Specification of Safety Parameters

Meditation-related risks: NCCIH states that meditation is generally safe for healthy people, but that adverse effects have also been reported. [5] Undesirable side effects and risks of meditation have been documented in more than 40 scientific reports [for reviews see [6-8]] and are listed in the Mindfulness-Based Intervention Guidelines.[9,10] More common, less serious side effects that

have been reported by individuals within the context of MBIs or of individuals who are meditating less than an hour per day include: increased depression, anxiety or panic, re-experiencing of traumatic memories, dissociation, executive dysfunction, headaches/body pain and insomnia.[6,11-16] A few case reports of more serious side effects including mania, psychosis, and suicidality have been reported, mostly in the contexts of intensive retreats (>5 hrs/day) or in conjunction with pre-existing psychopathology.[6,8,9,17] The frequency of serious adverse effects in the context of MBIs is estimated to be less than 1%, although adequate estimates are not available.[18]

A number of actions have been taken to minimize meditation-related risks at different stages of the study. During the pre-enrollment stage, individuals with severe mental illness are excluded from the study and all risks are clearly communicated in the consent form. During treatment, meditations are relatively short and interspersed with dyads and reflections. Mindfulness homework assigned as part of the intervention is optional and is recommended to not exceed 1 hour per day. Teachers query participants about their experiences with meditation, and provide corrective feedback or modifications when needed. Developing strategies for working with physical and emotional discomfort is an explicit goal of the program. Because not all participants feel comfortable disclosing difficulties in class, an online "safety check-in" questionnaire will query meditation-related risks (see section 6.2.1). Dr. Ellen Flynn, a licensed psychiatrist, will be available to advise on any psychological events that occur, and provide referrals for treatment if needed. Additionally, Dr. Willoughby Britton will provide expert consult on safety monitoring and reporting, including providing DSMP specific training to research staff and investigators.

Psychological distress: Research subjects participating in this study may have feelings of loss of privacy from being contacted about participating in the study, and possible psychological distress caused by questions asked during the in-person and online questionnaires that bring up painful memories or feelings. However, the resulting potential for injury to research subjects is judged to be minimal. We have already contacted and clinically evaluated thousands of participants from other studies such as the New England Family and Women's Health Initiative using similar assessment procedures to this study, with good responses from the participants. With regard to psychological distress from taking part in the MB-BP intervention, given that screening questions will exclude participants with substantial mental illness, and given the NCCIH statement above that "Meditation is considered to be safe for healthy people."[244] we expect that risk of psychological distress will be low. The risk of increased psychological distress from meditation will be clearly outlined in the consent form and participants will be encouraged to consult with both the course instructor and study staff in the case of any increased distress. Dr. Ellen Flynn, a licensed psychiatrist, will be available to advise on any psychological events that occur, and provide referrals for treatment if needed.

Loss of confidentiality: Likelihood: rare. Minimization: Confidentiality will be maintained by using deidentifying data sets. All paper forms and data collection tools, including the informed consent forms, will be kept in a locked filing cabinet in a secure location. All electronic data files containing identifying information will be encrypted with a cloud-based software. Note that although these measures have been taken to protect participants' personal information, complete confidentiality cannot be guaranteed when transmitting information over the internet. All information obtained from participants will be accessible only to research staff.

Injury due to physical activities: It is possible that injuries could be sustained from (1) the gentle mindful movements (yoga), or (2) physical activities that participants engage in as a result of the intervention encouraging exploration of physical activity as a way to reduce blood pressure. (1) Mindful movements: Participants receive a handout during the orientation showing the yoga

poses that will be offered during the course. They are encouraged to explore limits in their body related to movement, but not to go beyond those limits Participants are asked to listen to what their body is telling them more closely than what the mindful movement instructor is telling them. Modifications of poses are available, including for those limited to chairs or wheelchairs. Participants are encouraged to bring the handout of poses to their health care providers if they have any physical limitations, so that the providers can advise on which poses to do, and which to avoid. (2) Physical activities: Participants are encouraged to explore physical activities that promote strength and conditioning as a way to reduce blood pressure. As with the mindful movements, they are encouraged to explore limits in their body related to movement, but not to go beyond those limits. Participants are asked to listen to what their body is telling them more closely than what the mindful movement instructor is telling them. Furthermore, they are encouraged to ask their healthcare provider about advised physical activities if they have any physical limitations.

Risks associated with fMRI: The fMRI study will be conducted using a 3T MR scanner at UMass Medical School, which has been approved for research and clinical studies in children and adults by the FDA. Magnetic resonance (MR) technology does not use X-rays, but instead uses strong magnetic fields and radio waves. Individuals interested in participating in the fMRI study will complete a screening questionnaire to assess eligibility, including asking whether they have devices that can be affected by MRI or conditions (e.g., claustrophobia, body mass greater than 300 lbs.) that prohibit the ability to be scanned. Participants are screened immediately prior to each MRI scan to ensure participant safety. Significant risks also can arise if ferromagnetic materials are brought into the high magnetic field environment of the scanner and immediate vicinity, as they can become hazardous projectiles. These types of items are not permitted in the scanning area. The MR exams are painless, and except for the pulsating sounds, subjects will not be aware that MR scanning is taking place. With proper safety precautions in terms of the avoidance of metal objects, there are no known health risks associated with MRI. The safety of MRI is reflected in the fact that it is used in standard medical practice without the requirement for informed patient consent. Most people experience no ill effects from the magnetic field, but some report claustrophobia, dizziness, mild nausea, headaches, a metallic taste in their mouth, double vision, or a sensation of flashing lights. These symptoms are transient and resolve quickly after the subject exits the scanner. The technologist will be able to hear subjects at all times and subjects are free to end the procedure at any time. In rare cases, a very slight, uncomfortable tingling of the back due to the rapid switching of the magnetic field has been reported during certain types of scans. Subjects are asked to report this immediately so the scan can be changed to avoid this. Although these precautions will avoid all known risks associated with MR, this procedure may involve risks that are currently unknown. The scanner is noisy, but does not harm hearing. For comfort, subjects will be given earplugs to muffle the noise.

Risk of adverse events during the study: It is possible that some patients will have an adverse event during the study, including increased stress or anxiety. Participants with major mental health conditions, such as schizophrenia, history of psychosis, bipolar depression, suicidal ideation, borderline personality disorder, post-traumatic stress disorder, obsessive compulsive disorder, panic attacks, current alcohol or substance abuse, or an eating disorder are ineligible for the study. We expect risk of adverse events to be very low. For further discussion of AE and SAE monitoring and reporting refer to Section 6.2 below.

Impact statement: These risks are considered to be minimal and are addressed in the protocol and consent form.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Safety monitoring will occur continuously throughout the study using both active and passive monitoring methods outlined and discussed in further detail below. All reported AEs, SAEs, and unanticipated problems will be recorded throughout the study using the data collection systems set up and detailed in the Data and Safety Monitoring Plan (DSMP)

The research staff will record all reportable events with start dates occurring any time after informed consent is obtained but no later than the final 1-year assessment. At each study visit, the research staff will inquire about the occurrence of AE/SAEs since the last visit (or time of most recent reporting). Events will be followed for outcome information until resolution or stabilization or until the grant funding ends.

7.3 Adverse Events and Serious Adverse Events, Reporting Procedures, and Follow-up

An adverse event (AE) is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. A serious adverse event (SAE) is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Per NCCIH safety monitoring requirements, all AEs and SAEs captured and/or observed involving enrolled study participants will be recorded regardless of their relationship to the study intervention. Below we outline possible AEs and SAEs that may occur related to this research study and intervention; present our procedures for capturing and recoding; and detail the protocol for follow up of AEs. For further discussion of the procedures related to safety monitoring and follow up procedures refer to Section 7.4. Safety Monitoring.

Safety Check-ins: All participants enrolled in the study, regardless of treatment allocation, will receive a two-tiered safety monitoring ‘check-in’ every 2 weeks during the treatment phase of the study; every month during months 3-6 of the follow-up phase; and at the final 1-year time point. The two-tiered system is designed to detect and follow up on AEs that are at least moderate in severity (interfere with ADL), and to minimize staff and participant burden that would otherwise occur if all mild events were queried and documented.

Tier 1 of the safety check-in involves sending all active, enrolled participants an email (or placing a phone call from a research staff member, if no email provided) containing a link to a brief online survey that queries events with moderate or greater levels of severity. Any participant who endorses one or more tier 1 questions will automatically receive a tier 2 survey and follow-up phone call from study staff.

The Tier 2 survey specifically queries the most common meditation-related side effects (e.g. anxiety, depression, dissociation, flashbacks etc.) using patient-reported outcomes measurement information system (PROMIS) or NeuroQol items (or other validated scales if construct is not available), and PROMIS response options (never- very often).

Additionally, the tier 2 survey will ask participants to provide further detail (i.e., date of onset, symptomology, circumstance surrounding the event, relatedness to the intervention, etc.) regarding the AE/SAE reported in the tier 1 survey. Detail provided will be used to guide the tier 2 phone calls made by research study staff.

Tier 2 Safety Check-in phone call: Any participant who indicates that he or she experienced an AE or SAE will then receive a follow up call from a trained research staff member. The purpose of the follow up call will be to further document the details of the AE/SAE, assess need for treatment modification, referrals and reporting.

Research staff members conducting the safety monitoring phone interviews will document the details of the AE/SAE using the Adverse Events Form, which will then be included in the participant file as well as in the annual Data Safety Monitoring Reports presented to the DSMB. Reporting procedures for AEs and SAEs related to the study will be followed including reporting all SAEs to the study PI and DSMB committee chair.

7.3.1 Mental Health

Participants assigned to any treatment group may experience mental health or suicidal ideation during the course of their study involvement. All study participants will be monitored for AEs and SAEs by study staff on a monthly basis until the time of their study completion. Additionally, participants will be asked to complete questionnaires about anxiety, depression and suicidal ideation, specifically the Beck Anxiety Inventory and the Center for Epidemiology Study Depression Scale Revised (CESD-R), at each of their in-person assessments, excluding the one year follow up. Dr. Flynn, a licensed psychiatrist with extensive experience evaluating research participants for clinical deterioration or suicidality, will serve as the study clinician.

Beck Anxiety Inventory (BA): If participant scores ≥26 on the Beck Anxiety Inventory, a safety flag will appear notifying the research assistant (RA) administering the assessment. The RA will then implement the MB-BP safety protocol, which is reviewed and approved by the Brown University IRB. Staff are trained on the safety protocol and a hard copy of the protocol is kept in an accessible location in the assessment office at all times.

Depressive Symptomatology: The CESD-R will be administered during the in-person assessment visits, and scores will be reviewed immediately upon completion of the in-person assessments.

1. Sadness (dysphoria): Question numbers 2,4, 6
2. Loss of Interest (anhedonia): Question numbers 8, 10
3. Appetite: Question numbers 1, 18
4. Sleep: Question numbers 5, 11, 19
5. Thinking / concentration: Question numbers 3, 20
6. Guilt (worthlessness): Question numbers 9, 17
7. Tired (fatigue): Question numbers 7, 16
8. Movement (agitation): Question numbers 12, 13
9. Suicidal ideation: Question numbers 14, 15

Participants are considered to meet criteria for major depressive episode if they have anhedonia or dysphoria nearly every day for the past two weeks, plus symptoms in an additional 4 DSM symptom groups noted as occurring nearly every day for the past two weeks. If participants meet criteria for major depressive episode, a safety flag will appear notifying the research

assistant (RA) administering the assessment. The RA will then implement the MB-BP safety protocol, which is reviewed and approved by the Brown University IRB. Staff are trained on the safety protocol and a hard copy of the protocol is kept in an accessible location in the assessment office at all times.

If participants respond having any suicidal ideation (CES-D questions 14 or 15), staff will again be instructed to follow the IRB approved safety protocol.

7.3.2 Physical Health

Possible atrial fibrillation detected during Heartbeat Detection Task: If possible atrial fibrillation is indicated by the Kardia Mobile device during the "Heart Beat Detection Task" a safety flag will appear notifying the research assistant (RA) administering the assessment. The RA will then implement the MB-BP safety protocol.

Out-of-range blood pressure readings: If during an in-person assessment the participants systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) falls outside of the acceptable range outlined in the safety protocol, the RA will be notified and the IRB approved safety protocol will be implemented.

Injury due to physical activities: It is possible that injuries could be sustained from (1) the gentle mindful movements (yoga), or (2) physical activities that participants engage in as a result of the intervention encouraging exploration of physical activity as a way to reduce blood pressure.

(1) Mindful movements: Participants receive a handout during the orientation showing the yoga poses that will be offered during the course. They are encouraged to explore limits in their body related to movement, but not to go beyond those limits Participants are asked to listen to what their body is telling them more closely than what the mindful movement instructor is telling them. Modifications of poses are available, including for those limited to chairs or wheelchairs. Participants are encouraged to bring the handout of poses to their health care providers if they have any physical limitations, so that the providers can advise on which poses to do, and which to avoid.

(2) Physical activities: Participants are encouraged to explore physical activities that promote strength and conditioning as a way to reduce blood pressure. As with the mindful movements, they are encouraged to explore limits in their body related to movement, but not to go beyond those limits. Participants are asked to listen to what their body is telling them more closely than what the mindful movement instructor is telling them. Furthermore, they are encouraged to ask their healthcare provider about advised physical activities if they have any physical limitations.

Note that adverse events related to physical injuries will be captured during the routine safety check-ins (discussed above).

7.3.3 Other

Participant Initiated (Passive monitoring): Participants are encouraged to contact meditation instructors and/or study staff if any physical or mental health symptoms arise or other study or meditation-related problems occur. Participants may report AEs at any time throughout the study. Events will be evaluated with the Adverse Events Form by study staff.

Attrition: Reasons for attrition are also an important source of AEs, but are rarely assessed adequately, as participants are unlikely to give honest answers if queried directly by study staff. To increase the accuracy of attrition reason reporting, participants will be asked to complete a brief online Participant-initiated dropout reason survey (see Appendix A7).

Investigator-initiated withdrawals: In rare circumstances, a study participant may be withdrawn from the study and/or intervention by the researcher. In this case, the researcher or other study staff should complete the Attrition information form, and describe reasons for attrition. Note, however, that this scenario would be very unusual, and has not happened once in the in the approximately 130 participants who have gone through the MP-BP study to date. Potential reasons for investigator-initiated withdrawal would be MB-BP classroom or assessment disruption in ways that are causing harm or an unsafe environment for other classroom participants, the instructor, or study staff. The screening questionnaire excludes participants with mental health criteria that puts them at higher risk for disruption. We expect this scenario to occur extremely rarely (as evidenced to date), but remains a possibility.

fMRI Study Safety Monitoring: it is possible participants may experience or report an AE or SAE during their involvement with the fMRI Study. Research staff will use the Adverse Events Form and accompanying documents found in the Appendices to document all AE/SAE discovered at the time of involvement in the fMRI imaging study. The logged events will then be communicated to the Coordinating Center, so that they can be included in the participant file as well as in the annual Data and Safety Monitoring Reports presented to the DSMB. Reporting procedures for AEs and SAEs related to the study will be followed including reporting all SAEs to the study PI and DSMB committee chair.

Non-Response to Treatment: The possibility that the treatment will not yield benefit is another possible risk and will be explained during informed consent procedures. Non-responders (identified as minimal change in medical regimen adherence from baseline assessment) will be provided with referrals to other treatment, if desired.

The data collection systems we have set up to monitor and record AEs and SAEs are specifically designed to avoid double capture. Unique participant identifiers, dates and details surrounding events, as well as steps taken to follow up are recorded.

7.4 Safety Monitoring

Oversight of internal monitoring of the participants' safety will be conducted by the local PI, Dr. Eric Loucks. Oversight of the external Data and Safety Monitoring Committee will be conducted by the chair (Dr. Edmondson). The Data and Safety Monitoring Committee will include experts in cardiology (Choudhary), psychology/psychiatry (Edmondson), epidemiology (Choudhary), and biostatistics (Liu).

Entities Conducting Monitoring: The Institutional Review Board (IRBs) at Brown University will review all research procedures, and will provide oversight. Internal monitoring will be done by the Brown University principal investigator (Dr. Loucks) and the Brown University IRB. The Data Safety Monitoring Committee will provide external monitoring, and will meet annually by phone, video conference, or in-person. They will be provided data annually in order to evaluate potential effects of the RCT on major outcomes (e.g. medical regimen adherence). Any serious adverse effects will be immediately reported to the principal investigator (Loucks) and the committee chair.

What is Monitored: Monitoring is done of all procedures to ensure that they conform to the approved protocol; of unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined in US Department of Health and Human Services regulations for the protection of human research subjects 45 CFR Part 46, and the FDA 312.32 (death, life-threatening experience, new or prolonged hospitalization, persistent or significant disability/incapacity); of other significant adverse events (adverse events that lead to drop out by participant or termination by the investigator); of unexpected adverse events resulting from the study; and of expected adverse events.

Monitoring is done of all study inclusion and exclusion criteria. During this clinical trial, we will notify officials, as mandated by law, if a participant reports intention to harm him/herself or others, or reports child abuse or abuse of an elder. Dr. Ellen Flynn, a licensed psychiatrist, will be available to advise on any psychological events that occur, and provide referrals for treatment if needed.

Frequency of Monitoring: All adverse events will be continuously monitored by the PI as they are documented by the study staff in accordance with the protocol (Please see section 7.3). Participants will be given contact information so that they can inform us of events that occur in between study visits. The PI will meet with staff weekly as schedules allow to review participant progress and to check in about the experiences with the experimental procedures, including adverse events. Any adverse events that are observed and/or reported will be reported to Dr. Loucks and the Data Safety Monitoring Committee chair under the proposed timelines in the DSMP. The Investigators and DSMB members will be available to meet outside of the regularly scheduled meetings (scheduled annually), if necessary, due to concerns regarding a particular participant or any problems that may arise for participants. If necessary, they will make appropriate recommendations for changes in protocol, or terminate the study. The Brown University IRB conducts the monitoring at the continuing reviews as scheduled, whenever modification requests are considered, and upon receiving reports of serious adverse events from the PI or anyone else.

Reporting Plan: Any serious adverse events that are observed and/or reported will be immediately reported to Dr. Loucks and the Data Safety Monitoring Committee Chair. Serious adverse events related to the study are then reported to the Brown University IRB and to NIH. Brown University's IRB requires fatalities related to the study be reported within 24 hours. All serious adverse events related to this study will be reported to the Brown University IRB immediately by telephone and by written report within 48 hours of our receipt of information regarding the event. All other adverse events related to the study will be reported at the continuing review. Serious adverse events related to the study will also be reported in writing to the NIH Project Officer within 48 hours of the PI becoming aware. All serious adverse events related to the study will be reported annually in the Progress Report sent to the NIH Project Officer. Data on all AEs and SAEs will be recorded.

Any actions taken by the IRB, other than acceptance of the adverse event report, will be reported to the NIH along with any changes or amendments to the protocol requested by the IRB in response to these reports. Proposed changes or amendments to the protocol in general must be approved in writing by both the Brown University IRB as well as by the funding agency, NCCIH.

8. INTERVENTION DISCONTINUATION

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial.

9. STATISTICAL CONSIDERATIONS

9.1 General Design

Analyses will evaluate (1) whether MB-BP influences self-regulation targets, (2) whether the MB-BP-induced changes in self-regulation targets are associated with changes in medical regimen adherence, and (3) whether MB-BP is associated with medical regimen adherence. Analyses will incorporate generalized linear models (GLM) with properly chosen link functions, performed using generalized estimating equations (GEE) with robust standard error estimators.[245,246] This provides an extension of regression analysis to the case of correlated or repeated observations, allows for inclusion of both continuous and discrete dependent variables, and enables modeling of covariance structures when observations are correlated across time. Following “intention-to-treat” principles, analyses will be conducted on all participants in the randomized controlled trial, regardless of intervention completion. Analyses will use GLM with identity links for normally distributed data. The between-groups independent variable in the GEE analysis is intervention condition, with control conditions as distinct referent groups. Categorical variables will be included in GLM/GEE models as indicator variables with one level chosen as referent. Continuous independent variables such as age and baseline blood pressure would be included as linear terms. In addition, we will include assessment time as a linear term and possibly with an additional quadratic term to capture possible non-linear relationship of time with the outcomes. It is conceivable that one would observe a steeper slope in the initial months that would decrease in the pursuing months. Thus, the use of a quadratic term for assessment time would be able to capture these phenomena. To evaluate self-regulation targets as mediators of the effects of MB-BP on medical regimen adherence, mediation analyses described by Valeri and VanderWeele will be employed.[247] Such analyses will allow for potential interactions between the exposure and mediator of interest and account for potential confounders of the exposure-mediator, mediator-outcome, and exposure-outcome relationships using standard regression techniques. These methods estimate total, indirect and direct effect sizes, as well as statistical variance.[247]

9.2 Sample Size and Randomization

Treatment Assignment Procedures

Statistical Power:

Utilizing effect sizes and statistical variance from the Stage 1 MB-BP clinical trial showed an increase of MAIA from baseline of mean 22.6 (SD=6.5) to mean 26.3 (SD=6.0) at 6-month follow-up, demonstrating a 3.7 increase in MAIA score ($p<0.001$). Power analyses using the T statistic and non-centrality parameter, with alpha (two-tailed) set at 0.05 and beta at 0.2, shows with a MAIA increase of 3.7 in MB-BP vs. control, sample size requirements are 46 per group. With DASH diet score increasing from 2.78 (SD=0.61) at baseline to 3.37 (SD=0.81) at 6-month follow-up in the Stage 1 MB-BP study in the 67% of participants with a low DASH score (<5.5), demonstrating a DASH diet score increase of 0.59 ($p<0.001$). Using an effect size of 0.5, power analyses using the T statistic and non-centrality parameter

suggest that, with alpha (two-tailed) set at 0.05 and beta at 0.2, a sample size of 33 per group will be sufficient.

Using simulations from Fritz and MacKinnon,[248] for 80% power to detect a mediated effect when effect of exposure on mediator, and mediator on outcome, is of small to medium strength (standardized Cohen's d effect sizes of 0.26-0.39 each), based on Sobel first-order test, we will need 90 participants. Given that 67% of Stage 1 participants had DASH diet score <5.5, recruiting a sample size of 160 participants across the UH2 and UH3 phases (Figure 1), this would allow for 107 participants with low DASH diet to be included in primary mediation analyses with DASH diet score as the outcome. Stage 1 effect sizes on DASH diet score were large Cohen's d (d=0.82). Effect sizes on the primary self-regulation outcome was medium (MAIA Cohen's d=0.59). Assuming associations between the MAIA and DASH diet score are in the small to medium range, the study should be adequately powered for mediation analyses. Please note that Stage 1 analyses also demonstrated significant improvements in other health behaviors, including alcohol consumption and physical activity following the MB-BP intervention. Secondary analyses will evaluate impacts of MB-BP on these health behaviors, but are not adequately powered for mediation analyses due to the lower proportion of participants that do not adhere to these behavioral AHA guidelines (i.e. approximately 15% of participants do not comply to AHA alcohol guidelines, and 32% do not adhere to physical activity guidelines in our Stage 1 sample).

The fMRI imaging analyses (n=24 per group) should be adequately powered, based on power calculations shown in the MINDFUL-PC study below and by power calculations outlined in the fMRI study protocol and MOP. To achieve this, we estimate having to enroll up to 60 eligible study participants into the fMRI study.

For fMRI self-regulation neural targets, resting State Functional Connectivity (rs-FC) will be expressed as correlation coefficients, transformed using Fisher's z-transformation for analysis. rs-FC will be obtained at two time points (baseline: T1; post-training: T2) for participants and controls. We will use a mixed effects model with baseline rs-FC as an additional predictor for the change outcome. There are two elements to the hypotheses – the determination of the significance of the change within group and the comparison of the change in the treatment group compared to the control group. For the comparison in change between treatment and control group, with a mixed analysis of variance (within-subjects rs-FC at T1 and T2, and between-subjects according to intervention; sample size, total n = 48, 24/group), we are able to detect an ES of 0.3 between the two treatment groups with 81.3% power (and an ES of .21 with 81.3% power for within-group mindfulness effect; an ES of 0.23 with 87.7% power for an interaction of treatment and time), with two-sided tests at alpha=0.05. Thus is reasonable power to detect small- to moderate-size differences in BOLD.[249]

Our calculations assume drop-out rates will average around 10-15% across each group, with the control group exhibiting the highest rates of withdrawal and loss to follow up. These estimates are based on the Stage 1 and 2a MB-BP trials in the UH2 phase.

Randomization procedure: Please see Section 3 (study design) above.

Blinding protocol: Please see Section 3 (study design) above.

9.3 Definition of Populations

Please see Section 9.1 for Intention-To-Treat analysis approach.

9.4 Interim Analyses and Stopping Rules

Please see Section 8 for stopping rules and related analyses.

9.5 Outcomes

9.5.1 Primary Outcome

Self-Regulation Primary Outcome: Multidimensional Assessment of Interoceptive Awareness (MAIA), a validated measure of body awareness.[222-224] We hypothesize that MB-BP will significantly improve the MAIA in directions of better self-regulation, compared to control.

9.5.2 Secondary Outcomes

Self-regulation outcomes foster triangulation, including further validated measures of interoceptive awareness (Heartbeat Detection Task,[250,251] Interoceptive Awareness fMRI Task[252-254]), stress and emotion regulation (Difficulties in Emotion Regulation Scale,[221] Pittsburgh Stress Battery,[255-259] Perceived Stress Scale,[219,220] Beck Anxiety Inventory,[203-209] CESD-R[201,202]), attention control (Sustained Attention to Response Task,[228-233]), self-compassion (Self-Compassion Scale Short Form[121]), and self-efficacy (Self control scale and SECD-6 Scale[260-267]).

Medical regimen adherence outcome: Diet, assessed utilizing Dietary Approaches to Stop Hypertension (DASH) eating pattern score,[181] measured via diet history food frequency questionnaire.[182] The measure assesses adherence to JNC-7 guidelines DASH eating pattern score (range 0-8).[181,183]

Medical regimen adherence secondary outcomes: *(1) Alcohol consumption:* Amount and frequency of alcohol consumption, will be assessed via self-report utilizing standard questions from the behavioral Risk Factor Surveillance Survey.[184] AHA/ACC hypertension clinical practice guideline cut-point of healthy alcohol intake is ≤ 2 drinks (e.g. 24 oz. beer, 10 oz. wine, or 3 oz. 80-proof whiskey) per day in men and ≤1 drink per day in women.[10] Medical regimen adherence will be defined as adherence to JNC-7-recommended behavioral and medication treatment of hypertension.[183] *(2) Electronically-Measured Antihypertensive Medication Adherence:* measured continuously using electronic medication bottle caps (eCAPS, Ottawa, Canada)[185] *(3) Body Mass Index:* height and weight directly assessed using standard epidemiologic methods, with change evaluated in participants considered overweight or obese (BMI≥25 kg/m^2).[186] *(4) Physical activity:* We will use the International Physical Activity Questionnaire which has undergone substantial validity and reliability testing.[187-189] Adherence to Joint National Commission-7 (JNC-7) guidelines is 30 min aerobic physical activity ≥4 days per week.[183]

9.6 Data Analyses

Please see Section 9.1 for analytic approach.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Questionnaire data will typically be collected using Qualtrics, LLC (Provo, UT, USA) survey instruments, so that participants can complete questionnaires on their own time at home within the defined assessment windows, using their computers or smart phones. Exceptions to this include the phone screening questionnaire, and the baseline and follow-up questions on depression and anxiety (described in Section 6.2.2) to allow for a safety protocol to be followed if there are high levels of depression, anxiety or suicidal ideation. In the event that participants are uncomfortable or unable to use a computer for tests data will be collected using hard copies of surveys and entered by a trained member of the research staff.

Assessments of blood pressure, height, weight, and medication use are assessed in-person by trained research assistants blinded to treatment allocation.

Confidentiality of Patient Records: The clinical data will be de-identified but linked. Private information such as name, date of birth, and address for recontacting will be kept in a password protected, encrypted database on a different disk than the clinical data held by the Project Coordinator and used for the purposes of contacting participants. The principal investigator will only be given access to identifiable personal information for the purposes of patient safety or monitoring by the NIH, data safety monitoring boards or HIPPA compliance officer approved agents.

10.2 Data Management

Data management will be performed by downloading data at minimum every 2 weeks during active data collection periods, and assessing data for missingness and errors. Data will be maintained in password-protected Microsoft Excel Spreadsheets, and then exported using .csv functions for analysis in SAS software.

Please see Section 10.1 for data collection forms description.

10.3 Quality Assurance

10.3.1 Training

Describe types and mechanisms of training of staff for the study.

Please see **Appendices E and F** for manuals to perform staff training for assessments. Only trained, experienced, culturally competent interviewers will be hired to perform assessments.

10.3.2 Quality Control Committee

There is no formal quality control committee.

10.3.3 Metrics

Please see Appendices E and F for quality control metrics of blood pressure and anthropometry assessments.

MB-BP Competency and Treatment Fidelity: Treatment fidelity strategies will be performed in accordance with recommendations of the NIH Behavior Change consortium, specifically ensuring treatment fidelity in the following five areas: study design, training providers, delivery of treatment, receipt of treatment and enactment

of treatment skills,[268] as follows. *Study design*: All session durations will be recorded and any deviations from the planned duration will be documented. All class sessions will be taped (as conditions allow). Audiotapes will undergo a quality assessment audit by research technicians, who will review a ten percent randomly selected sample of the recordings. Research staff completing the audit will conduct competency ratings on these tapes using validated adherence scales (MBCT Adherence Scale, where items 1-11 in the scale are for MBSR, MB-BP and MBCT[269]). Data from the audit will be used to provide detailed feedback to treatment providers. We will ensure equivalent dose across conditions, including meditation, yoga and stress reduction training, through tracking the audio recordings. Possible setbacks in implementation of treatment will be addressed, including having a large pool of MBSR and MB-BP instructors in the event that specific instructors no longer teach classes. Instructor attrition will be tracked.

Provider training: MB-BP will be performed by qualified or certified MBSR instructors[191] with formal training in cardiovascular health (e.g. dietician, physician assistant, health and wellness coach, and those with an Associate's or Bachelor's degree in relevant health sciences), and further certification in MB-BP. MB-BP instructor training involves: (1) An initial 40 hour in-person or online videoconference training where the unique elements of MB-BP are introduced. (2) Two half-day in-person training retreats where MB-BP-specific teaching modules are practiced in peer groups, supervised by the senior MB-BP trainer, with peer and trainer feedback. (3) Studying specific evidence-based articles on hypertension etiology, treatment and prevention, as well as articles synthesizing evidence of mindfulness on hypertension and hypertension risk factors. [10,183,192-194] A written exam evaluates knowledge in this area, for which instructors-in-training need to pass. (4) Supervised teaching of MB-BP in non-study participants is done using the Mindfulness-Based Intervention Teacher Assessment Criteria (MBI-TAC), [1,2,195] and an annotated MB-BP Curriculum Guide until adequate quality is established within predefined criteria.

MBSR teacher certification is fairly extensive, and accreditation occurs through the University of Massachusetts Medical School Center for Mindfulness in Medicine, Health Care and Society, detailed elsewhere.[191] Examples of criteria for becoming a certified MBSR teaching include (i) completion of an eight-week MBSR course as a participant, (ii) completion of several multi-day residential training courses in mindfulness based stress reduction practice and teaching, (iii) substantial experience in teaching MBSR, (iv) strong references letters from colleagues and participants who have taken your MBSR courses, (v) completion of several multi-day mindfulness meditation retreats, (vi) have a graduate degree in a field connected to MBSR (e.g. education, psychology, medicine) or demonstration of equivalent understanding through work experience in a related field. There are 89 registered MBSR programs in Massachusetts (60), RI (9) and CT (20) that offer year-round program including the Center for Mindfulness where MBSR originated. Eligible programs must be 8 weeks and the instructors must have completed the MBSR Instructor certification training to participate in the study.

Delivery of treatment: We will assess participants' perceptions of provider warmth and credibility using brief measures based on the validated Working Alliance Inventory,[270] and Therapist Empathy Scale[271] at Weeks 4 and 8 of the intervention. Feedback will be provided to the interventionist, and measures of warmth and

credibility will be adjusted for in sensitivity analyses, to evaluate if results differ when these measures are included vs. excluded.

Receipt of treatment and enactment of treatment skills: Adherence to the prescribed MB-BP practices will be monitored through class attendance, practice logs and diaries. Adherence data will be collected weekly during the course of the intervention. Mindfulness will also be measured through the use of the validated Five Facet Mindfulness Questionnaire[218] as well as by asking about at home mindfulness practices post-intervention.

10.3.4 Protocol Deviations

Protocol deviations will be reported to the Brown University IRB and NCCIH. A description of the deviations, and any effects on the protection of human subjects will be documented. Investigator(s) will review protocol deviations and determine on a case by case base which data (if any) will be excluded from the final data set.

10.3.5 Monitoring

Please see Section 10.3.4. for description of the monitoring approaches.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The protocol, the informed consent document (**Appendix D**), and any subsequent modifications, will be reviewed and approved by the Brown University IRB responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A signed copy will be offered to each participant and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

The clinical data will be de-identified but linked. Private information such as name, date of birth, and address for recontacting will be kept in a password protected, encrypted database on a different disk that the clinical data help by the Project Coordinator. All paper-based records (i.e. signed consent forms) will be kept in a secure physical location (e.g., locked filing cabinet). All computer entry and networking programs will be done using PIDs only. The principal investigator will only be given access to identifiable personal information for the purposes of patient safety or monitoring by the NIH, data safety monitoring boards or HIPPA compliance officer approved agents. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIH, and the OHRP.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research

participants are protected.

12. COMMITTEES

Data Safety Monitoring Board:

Oversight of internal monitoring of the participants' safety will be conducted by the PI, Dr. Eric Loucks. Investigators on this application have extensive experience with clinical trials for mindfulness-based interventions and cardiovascular health outcomes. Oversight of the external Data and Safety Monitoring Committee will be conducted by the chair, Dr. Donald Edmondson, PhD, who is Assistant Professor of Behavioral Medicine at Columbia University Medical Center. He is a Psychologist, and has extensive research experience in evaluating effects of stress and psychosocial factors on cardiovascular disease outcomes, along with clinical trials methods expertise.

The Data and Safety Monitoring committee will also include a board-certified cardiologist, Dr. Gaurav Choudhary, and a biostatistician, Dr. Tao Liu. Dr. Choudhary, MD, is Associate Professor of Medicine at Brown University. He is a practicing clinical cardiologist with research in epidemiology and cardiology. He will be able to advise on clinical outcomes and any cardiovascular complications arising from the study. Dr. Liu, PhD, is an Associate Professor of Biostatistics at Brown University, experienced in clinical trials. He will receive all preliminary analyses from the primary statistician, and will have access to all data from the study, to evaluate any evidence of serious adverse effects or other concerns.

These individuals are not associated with this research project and thus work independently of the PI. They are also not part of the key personnel involved in this grant. They are qualified to review the patient safety data generated by this study because of their unique expertise in the areas of cardiology, psychology/psychiatry, epidemiology, and biostatistics.

Entities Conducting Monitoring

The Institutional Review Board (IRBs) at Brown University will review all research procedures, and will provide oversight. Internal monitoring will be done by the principal investigators (Dr. Loucks) and the Brown University IRB. The Data Safety Monitoring Committee will provide external monitoring, and will meet every six months by phone or in-person. During the randomized-controlled trial phases (phase 3 & 4), they will be provided data every six months to evaluate potential effects of the RCT on the primary outcome (i.e. medical regimen adherence). Any serious adverse effects will be immediately reported to the principal investigator (Loucks) and the committee chair (Edmondson).

13. PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCIH prior to submission.

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15. SUPPLEMENTS/APPENDICES

Note that minor modifications may be made to the individual documents listed in the appendices during the course of the study.

Appendix A **MB-BP Curriculum Guide**

Appendix B **MBSR Curriculum Guide**

Appendix C **MB-BP Phone Screener (verbal consent process)**

Appendix D **MB-BP Informed Consent**

Appendix E **Anthropometric Quality Control Manual**

Appendix F **Blood Pressure Quality Control Manual**