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Principal Investigator:	Elena Salmoirago-Blotcher, MD, PhD

Exploring the role of mindfulness training in the promotion of medication adherence in heart failure outpatients.

Study Protocol

Principal Investigator

Elena Salmoirago-Blotcher, MD, PhD, FAHA

Division of Behavioral and Preventive Medicine
The Miriam Hospital

Assistant Professor of Medicine & Epidemiology

Warren Alpert Medical School and School of Public Health

Brown University

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The National Heart Lung and Blood Institute

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Tool Revision History

Version Number: 1
Version Date: 3-21-2018
Summary of Revisions Made: n/a

Version Number: 2
Version Date: 7-30-2018
Summary of Revisions Made:

- Adherence inclusion criteria modified
- Pittsburg Sleep Quality Index, Voils adherence assessment, program evaluation survey, Five Facets of Mindfulness, phone screening script added to study instruments/measures
- Morisky scale and SF-8 no longer included in study surveys

Version Number: 3
Version Date: 10-19-18
Summary of Revisions Made:

- Minor amendment to protocol to incorporate obtaining physician clearance for participant eligibility purposes.
- Physician Clearance form & fax cover sheet added to study instruments for approval
- Phone Screen updated with physician clearance criteria for approval (stamped, tracked and clean versions attached)
- Participant home practice log updated to incorporate two recordings instead of three (tracked & clean versions attached)

Version Number: 4
Version Date: 10-30-18
Summary of Revisions Made:

- Minor amendment to protocol to incorporate obtaining confirmation of a diagnosis of heart failure for patients recruited from the community.
- Minor protocol amendment to add "Statin" as an additional medicine which will qualify as a medication to be monitored.
- Confirmation of heart failure form added to study instruments for approval
- Phone Screen updated with heart failure confirmation for approval (stamped, tracked and clean versions attached)
- Participant home practice log updated to incorporate two recordings instead of three (tracked & clean versions attached)
- Requesting to add authorization/release form to give to patient in order for their physician to confirm a heart failure diagnosis.

Version Number: 5
Version Date: 3-5-19

Summary of Revisions Made:

- Removing staff (Rachel Kelly) from personnel & protocol. They are no longer assisting on project
- Updating Preparatory to Research & HIPAA Waiver of Authorization to remove staff that is no longer with the project

Version Number: 6
Version Date: 4-9-19

- Changes to adherence inclusion criteria
- Administrative modifications to study instruments and consent form where indicated

Version Number: 7
Version Date: 4-10-20

- Due to COVID-19 Pandemic, minor amendment to protocol to collect 3M & 6M follow up survey data over the phone, online, or by mail.

1 RESEARCH TEAM

Name	Role
Elena Salmoirago-Blotcher	Principal Investigator
Kristen Walaska	Project Director
Dyuti Trivedi	Research Assistant
Christopher Breault	Data manager
Shira Dunsiger	Biostatistician
Beth Bock	Co-Investigator
Ronald Cohen	Co-Investigator
Jia-Rong Wu	Co-Investigator
Daniel Levine	Co-Investigator
Priscilla Szneke	Mindfulness Instructor
Erin Sharaf	Mindfulness Instructor
Carole Legro	Mindfulness Instructor

2 LIST OF ABBREVIATIONS

AE	Adverse Event
AHA	American Heart Association
BOMC	Blessed Orientation Memory Concentration test
CBPM	Centers for Behavioral and Preventive Medicine
Co-I	Co-Investigator
FFMQ	Five Factors of Mindfulness Questionnaire
IMC	Independent Monitoring Committee
MAIA	Multidimensional Assessment of Interoceptive Awareness
HADS	Hospital Anxiety and Depression Scale
HF	Heart failure
HIPAA	The Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
MBSR	Mindfulness Based Stress Reduction
MT	Mindfulness training
PCP	Primary Care Provider
PHI	Protected Health Information
PI	Principal Investigator
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
RA	Research Assistant
TMH	The Miriam Hospital

3 BACKGROUND AND RATIONALE

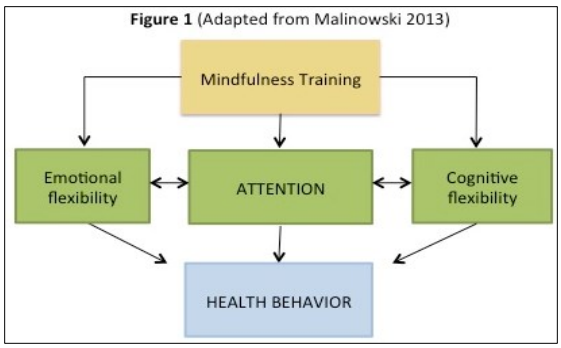
3.1. Background

Heart failure (HF) is characterized by the heart's inability to pump the necessary amount of blood to the peripheral tissues.[1] The prevalence of HF is increasing worldwide; in the United States alone, 5.7 million individuals are currently affected.[2] The most common causes of HF are atherosclerotic coronary heart disease, hypertension, diabetes, and the metabolic syndrome. Symptoms include shortness of breath, fatigue, limited exercise tolerance, and fluid retention.[3] Although clinical outcomes improve with medical therapy,[4] HF has an unfavorable prognosis, with hospital re-admission rates of 50% within 6 months of discharge[5,6] and mortality rates of 50% within 5 years of the initial diagnosis.[1,7,8] Hospitalizations cost an average of $23,000 per patient[9] and combined costs for HF treatment reached almost $31 billion in 2012. A number of medications improve HF symptoms and significantly reduce re-hospitalizations and mortality.[4,10] Pharmacological treatment, however, can ultimately be effective only if patients take their prescribed medications regularly. Unfortunately, only 50% of HF patients are adherent to prescribed pharmacological treatments[11] and adherence tends to decline even among patients who are initially adherent.[12-14] Poor medication adherence has serious consequences, including higher rates of hospital re-admissions,[15] emergency room visits,[16,17] and mortality.[18-20]

3.1.1. Factors associated with poor medication adherence in HF patients. Cognitive impairment is a strong predictor of poor adherence and is highly prevalent in this population, affecting about 60% of patients.[21,22] A recent large prospective cohort study (n=309) conducted among community-dwelling patients with HF and no history of dementia found that poorer cognitive function predicted poor medication adherence independent of important covariates (depressed mood, social support, and disease severity). Memory and attention lapses reduce the patients' ability to develop consistent adherence patterns and have been significantly associated with poor medication adherence.[11,23-26] In addition to cognitive impairment, depression is also highly prevalent among HF patients and contributes to the poor medication adherence observed in these patients.[11,23,24,27-29 30]

3.1.2. Gaps in current knowledge. A review by the Agency for Health Care Research and Quality found that policy-level interventions to reduce out-of-pocket expenses, case management, and educational interventions were the most effective approaches to improve adherence to medications.[31] Such approaches, however, often do not address important patient-level factors such as cognitive impairment and depression and have not been universally effective. A Cochrane review of 182 randomized controlled trials (RCTs) found inconsistent effects across studies and small-to-medium effect sizes.[32] Of studies conducted among HF patients, 7 showed an improvement in medication adherence[33-39] but only 4 showed an effect on clinical outcomes, and most studies did not include objective assessments of medication adherence.[33-35,38] Further, studies often employed complex interventions with limited scalability and sustainability in "real life" clinical circumstances.[32,40] Clearly, more comprehensive, scalable approaches addressing patient-level determinants of medication adherence are needed.

3.1.3. Mindfulness training (MT) and medication adherence. MT involves learning to notice to which object the attention is drawn to at any given moment and to re-direct attention to the breath (or to any other chosen focus of attention) and is, in essence, a form of intensive



attention training.[41] Although the potential effect of MT on medication adherence has been purported as a possible mechanism by which MT could improve cardiovascular health,[42] no studies have yet formally investigated the possible effect of MT on adherence among patient with cardiovascular disease and data are scarce also in other populations. Results from a pilot RCT of Mindfulness-Based Stress Reduction (MBSR) in HIV-infected youth have shown that the intervention group was more likely to have a lower viral load at follow-up (p = .04) compared to the control group, a finding that was interpreted as due to improved ART adherence.[43] Observational evidence generated from our group (detailed in C.1) and others shows that higher mindfulness skills are associated with higher medication adherence and that MT can improve self-reported medication adherence in patients with stable cardiovascular disease.[44,45] We also note that both observational and experimental studies have shown that MT improves attention and working memory, which, as explained above, are important predictor of poor adherence in HF patients. Specifically, the initial phases of MT, which emphasize concentration practices (i.e., focusing the attention on the breath or another chosen object of attention) have been shown to improve attention skills.[46-48] A RCT of a 2-week MT intervention has shown that MT improved working memory capacity and reduced the occurrence of distracting thoughts during completion of the graduate record examination in graduate students. [49] Jha et al. observed an increase in working memory capacity among military personnel who underwent an 8-week mindfulness intervention compared to both military and civilian control groups. [50] A study conducted among experienced meditators showed better performances on measures of attention compared to controls without meditation experience.[51] Finally, a RCT has shown significant improvements in mindfulness skills and in measures of executive function among 201 older adults trained in MBSR compared to a wait-list control group.[52] There is also robust evidence that MT can improve depression, another important predictor of poor adherence in HF patients.[53-56]

3.1.4. Conceptual model linking MT and medication adherence. The conceptual model proposed for this study builds upon the model proposed by Malinowski and others, [57-60] on meta-analytical studies of the mechanisms of the efficacy of MT on health outcomes,[61] and on empirical evidence supporting of the efficacy of MT on attention and working memory.[46-51] In the proposed model, the refinement of attentional skills is central to the development of the cognitive and emotional flexibility needed to bring about changes in health behaviors (in our case, adherence to medications) (Figure 1). In this study, we are particularly interested in exploring pre/post intervention effects of MT on measures of attention and working memory and whether such changes are associated with changes in adherence. A full mediational analysis is beyond the scope of this study and thus, these analyses will be only exploratory. If results from this exploratory study are promising, this model will be tested in a fully powered randomized controlled trial (RCT), which will formally investigate the efficacy of MT on medication adherence as well as the mediating role of emotional (i.e., depression) and cognitive (attention, working memory) factors in bringing about changes in the tar

4 STUDY AIMS

Aim 1: To determine the feasibility and acceptability of mobile phone-delivered MT in HF outpatients. Hypothesis: We will be able to reach our recruitment goal (n=50) within the study timeline, with < 20% drop out rates by the end of the study and > 80% of participants reporting high (=grade 4) enjoyment ratings on a scale from 0 to 4.

Aim 2: To determine whether mobile-delivered MT can improve self-reported and objectively assessed medication adherence as well as functional capacity (a clinical marker of medication adherence, per PA requirements). Hypothesis: we will observe significant pre-post intervention improvements in medication adherence and functional capacity.

Aim 3: To explore whether memory and attention change over time and whether such changes are associated with changes in medication adherence. The goal is to explore potential mediating effects that will be formally tested in a future fully powered RCT. We hypothesize for example, that MT will improve working memory, and that such changes will in turn be associated with improvements in adherence. Although measures of memory and attention are our primary posited mediators, we will also explore the role of mindfulness and depressive symptoms (additional potential mediators of MT effect).

5 SAFETY ASSESSMENT

5.1. Overview.

Mindfulness training is a behavioral, low-risk intervention. Thus, we anticipate that patients will incur minimal risks due to their participation in this study. Potential untoward events that may occur include:

a. Emotional discomfort during mindfulness practice
b. Transient, mild discomfort during awareness of breath practice
c. Breach of confidentiality

The level of risk for each of these events is minimal.

5.2. Expected Risks and Protection Against Risks

a) Emotional discomfort during mindfulness practice is a rare occurrence. When occurring, it is mild, of short duration, and rarely occurs in absence of ongoing serious psychiatric conditions. Measures for protection will include:

- Participants with severe depression or ongoing psychosis will be excluded from participation in the study.
- In case a patient presents signs of severe psychological discomfort during or between sessions, he/she will be excused from participating in the mindfulness intervention. The instructor will inform the RA and conduct an assessment of suicidality (see Suicidality Assessment Protocol). The mindfulness instructor will actively inquire about psychological side effects that might occur during the session or during individual

practice. Mindfulness instructors are experienced and trained on how to help individuals presenting such issues. Participants will also be instructed to contact the RA should any discomfort arise during the training.

b) The likelihood of loss of privacy or confidentiality is rare and its impact on participants is likely to be minimal. Risks to privacy and confidentiality associated with this study will be described in the consent form along with our procedures to minimize this risk.

- Confidentiality of study data will be maintained by numerically coding all data, by disguising identifying information, and by keeping all data in locked file drawers. All information obtained from participants will be accessible only to research staff. In weekly staff meetings when study procedures are reviewed and issues of compliance are raised, participants will not be identified by name unless necessary, and then, only by first name and only to the study personnel who require this information.
- Audio recordings of mindfulness classes will be reviewed promptly to ensure treatment fidelity and then destroyed. Checklists and paper records of the treatment fidelity review will not include identifying information but will be stored and handled using the same methods as with other paper data.
- Study staff will maintain participant privacy by conducting phone interviews in private offices, by securing records in locked cabinets and by using password-protected databases. Project staff meetings will be held in private conference rooms. Instructions for maintaining privacy and confidentiality will be given to participants at the start of the first mindfulness class. In addition, participants will be reminded of these instructions and to respect each other's privacy and not repeat information shared with the group outside of the study setting.

5.3. Expected Benefits

The proposed research may result in direct benefits to participants and we expect that these benefits will outweigh the minimal risk associated with participating in this research study. Individuals who complete the mindfulness training may experience reduced levels of distress and an improved quality of life. [62] The magnitude of the benefit may be mild to moderate, and such benefits may last for the duration of the intervention and for the following months.

6 DATA AND SAFETY MONITORING PLAN

Several different entities will safeguard the participants' safety and the integrity and quality of the data.

- **Institutional Review Board (IRB)**: The study is submitted for approval and will meet all IRB requirements and directions.

- **The PI** will closely supervise all study activities. Dr. Salmoirago-Blotcher will meet weekly with the RA and the data manager to monitor recruitment procedures, accrual and retention, side effects, and data integrity in order to take the necessary measures in a timely fashion.
- **Independent Monitoring Committee (IMC):** Consistent with NIH guidelines for smaller studies (see: http://nccam.nih.gov/grants/policies/data-safety-monitoring) an IMC will be responsible for monitoring the safety of participants and the validity and integrity of the data. IMC members will include a biostatistician and an expert in mindfulness. The IMC will meet once a year, either in person or via conference call. However, the IMC will convene on a more frequent basis should urgent study concerns arise. At both scheduled and ad hoc meetings, the IMC will review adverse events, re-evaluate measures for the protection of human subjects if needed, and re-assess the risk/benefit ratio of the study. A report will be compiled after each meeting and will include (a) a list of adverse and serious adverse events classified by severity and likelihood of being related to the study intervention; (b) whether adverse event rates are consistent with pre-study assumptions; (c) rates and reasons for study withdrawal; (d) whether all participants met entry criteria; (e) whether continuation of the study is justified. Summary reports of IMC meetings will be sent to the PI and to the IRB and included in the annual reports for the project.

Study safety and progress will be monitored according to the schedule outlined in table1 (more frequently if needed).

Table 1.	**Frequency of data collection**	**Frequency of data review**	
Data type	**RA**	**PI**	**IMC**
Accrual, retention and attrition	Weekly	Every 2 weeks	Every 12 months
Adverse events*	Weekly	Weekly	Every 12 months
Participants' compliance to the intervention protocol	Weekly	Every 2 weeks	Every 12 months
Providers' compliance to intervention protocol	Weekly	Every 2 weeks	Every 12 months
Missing data/data integrity	Weekly	Every 2 weeks	Every 12 months

*** Please note: serious adverse events will be reported within 24 hours to the IMC, IRB, and to the sponsor in accordance with their requirements.**

6.1. Adverse Events and Serious Adverse Events

a. Definition. An adverse event (AE) is defined as any untoward medical occurrence in a participant temporally associated with participation in the clinical study. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.) or any combination of these. A Serious Adverse Event (SAE) is any adverse event that results in one or more of the following outcomes:
   - Death
   - A life-threatening event
   - Inpatient hospitalization or prolongation of existing hospitalization
   - A persistent or significant disability/incapacity

- Important medical event based upon appropriate medical judgment

Note: A birth defect is a highly unlikely event considering the age of our population. This outcome has been excluded.

b. Classification of AE Severity. AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed 'mild' if it does not have a major impact on the patient, 'moderate' if it causes the patient some minor inconvenience and 'severe' if it causes a substantial disruption to the patient's wellbeing.

c. AE Attribution Scale. AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled either definitely, probably, possibly or unrelated to the study intervention. The determination of whether an AE is related to the study intervention will be made by the PI. If relatedness is unclear, the PI will seek the guidance of the study cardiologist.

Reportable and non-reportable events. The IRB requires reporting of all SAEs as well as of those AEs that are unanticipated and related to the study protocol or procedures (that is, they are "unlikely", "possibly", "probably" or "definitely" related). Unanticipated AEs are events, signs and symptoms that are not listed as risks on the consent form. Please note that AEs that are either anticipated or are "definitely not" related to the intervention procedures ***are not reportable to the IRB at TMH***.

6.2. AE Reporting Procedures and Follow-Up

All *reportable* (see 6.1. for definition) *adverse events (AEs*) will be reported by the PIs to the IRB at TMH. Serious adverse events (SAEs) are reported to the IRB within 24 hours as described below ("SAE reporting"). All other reportable adverse events will be reported during the routine annual continuation reports to the IRB. In addition, all AEs (reportable and non-reportable) will be provided to the Chair of the IMC prior to each meeting.
All intervention visits (mindfulness sessions) and follow-up assessments will include proactive assessments of potential adverse events. The RA will record all AEs and SAEs in a secure database using the format in the example below:

Subject Identifier	AE Onset	AE End	AE Code	Severity	SAE? (y/n)	Relatedness	Action Taken	Outcome	Comments
Subj001	11/1/15			1	N	2	1	1	Subject felt anxious during MT; resolved within 15 minutes
Subj002	12/3/2015			2	N	3	1	1	Dizziness during exercise session
Subj003	12/18/15			3	N	0	4	4	Subject fell while hiking; broke leg; withdrew from study
Severity of AE:		**Relatedness to**		**Action Taken**:				**Outcome**:	

1 = Mild 2 = Moderate 3 = Severe 4 = Life threatening or disabling	**intervention**: 0 = Definitely unrelated 1 = Unlikely 2 = Possibly related 3 = Probably related 4 = Definitely related	0 = None 1 = Intervention modification 2 = Medical intervention (specify in comments) 3 = Hospitalization 4 = Intervention discontinued 5 = Other (specify in comments)	1 = Resolved 2 = Recovered with minor sequelae 3 = Recovered with major sequelae 4 = Continuing treatment 5 = Condition worsening 6 = Subject death

Participants will be asked about all AEs at each intervention session and at each follow up assessment. AEs will be recorded on the AE log and noted on the CO form. The RAs will report all AEs to the PIs as soon as possible. All AEs will be assessed to determine their classification and whether they meet criteria for an SAE. The study RAs will refer participants to their own physician for assistance with adverse symptoms. Each week the PIs will review AE reports from the previous week for events that were reported as new or continuing and will follow all AEs to the point of a satisfactory resolution. The PIs will be available at all times to discuss other adverse symptoms with the RA and the study participants.

SAE Reporting. SAEs that are unanticipated, serious, and/or possibly related to the study intervention will be reported to the IMC, the IRB at TMH, and to the sponsor (NHLBI) in accordance with their requirements (see 6.1).

Stopping rules. Considering the low-risk of this study, stopping rules have not been established. However, the IMC will closely monitor the risk/benefit ratio and the progress of the study and should issues in accrual, retention, data quality or safety arise, will take prompt action including considering the interruption of the study. Given the low risk of this study, no interim analyses are proposed.

6.3. Monitoring of Study Progress (Table 1)

Accrual, retention. Review of the number of screened and eligible participants/month, accrual rates, adherence to inclusion/exclusion criteria will occur weekly. This will help evaluate the adequacy of the eligibility criteria and of the recruitment procedures and to address concerns in a timely fashion.

Compliance with the intervention protocol. Protocol compliance will be assessed in an ongoing fashion. Participants' compliance will be monitored by the instructors and research assistant and will involve tracking of the number of sessions attended and of the total time of individual mindfulness practice. Instructors' compliance will be supervised by Dr. Salmoirago-Blotcher according to the Treatment Fidelity Workgroup guidelines. At the end of each MT session the instructor will complete a checklist in which duration and delivery of the intervention as specified in the intervention script will be evaluated, as well as the patient's level of engagement during the session. In order to monitor the consistency of the delivery of the intervention, each session will be digitally recorded. Ten percent of all recorded sessions will be randomly reviewed.

Data accuracy. The RA and data manager will be responsible for tracking participants to ensure that all data are collected in a timely and efficient fashion; for developing and generating monitoring reports; for providing timely and relevant feedback to the project leadership regarding the accuracy and precision of data. The following data verification procedures are planned:

Research Electronic Data capture (REDCap) technology will be used to for direct data entry during the interviews. REDCap employs automatic checks for values that are out of range or represent errors of logic. Outliers will be corrected with verification from participants.

Calculations (i.e., from self-report measures, when necessary) will be independently performed by two different persons and any invalid score (i.e. scores that differ between the two people) will be recalculated.

7 ELIGIBILITY

7.1. Population

Participants (n=50) will be recruited from the HF clinic at Rhode Island Hospital (RIH), located in Providence, RI as well as among community dwelling adults in the Providence area.

Vulnerable populations. This study will not recruit individuals from vulnerable populations (i.e.: adults unable to consent, Infants, children, teenagers or pregnant women). Subjects with severe cognitive impairment (and thus, unable to provide informed consent) are excluded from participation in the study (see 9.2 for details).

7.2. Inclusion Criteria

Participants must meet all of the following inclusion criteria to participate in this study (see sections 9.1 and 9.2 for a description of the screening visit and of the screening assessments):

- Age >18
- Fluency in English language
- A diagnosis of HF (based on medical record or confirmation from participant's physician)
- Access to a telephone
- Ability to understand and speak English

7.3. Exclusion Criteria

Participants must meet all of the following exclusion criteria to participate in this study:

- Unwillingness/inability to provide informed consent
- New York Heart Association[63] (NYHA) class IV heart failure or clinically unstable
- Severe hearing impairment not allowing phone delivery
- Severe depressive symptoms (defined as Hospital Anxiety and Depression Scale [HADS] depression subscale scores >14)
- Acute psychosis (from medical record)
- Severe cognitive impairment (BOMC[79] scores > 10)
- Unable to obtain confirmation of HF diagnosis
- Recent hospitalization (< 6 weeks)

- Current (at least once a month) mind/body practice (i.e., mindfulness meditation, yoga, or tai chi)

8 ENROLLMENT

8.1. Participants' Recruitment

Recruitment approaches will include the following:
1) The recruitment research assistant will identify patients scheduled for a visit at the Heart Failure Clinic at RIH (a HIPAA waiver and HIPAA preparatory to research requests are attached to this application). Patients will receive an invitation letter signed by the PI and Dr. Levine and a copy of the consent form either in person after their visit or by mail. The invitation letter will not contain any PHI nor personal identification. This package will be sent from the CBPM and mailed by study staff.
2) Flyers placed in clinics and in local public venues (e.g., community centers, libraries, supermarkets)
3) Social media (e.g. Facebook and Twitter) and on-line resources (hospital intranet; Craig's List)
4) Lifespan physician referrals
5) For items 2 & 3 physician clearance will be needed to confirm a medical diagnosis of Heart failure per study inclusion criteria.
All study recruitment materials will be submitted to IRB for approval.
We will track returns from the different recruitment venues in order to identify the most efficient recruitment strategies for the future RCT.

8.2. Screening and Consenting Procedures

Interest assessment phone call: Initial contact will be made via telephone by interested individuals using a dedicated phone number that will be included in the invitation letter and all recruitment materials. Individuals calling about the study will be screened by the study RA in a phone conversation to determine initial eligibility. The RA will briefly describe the study and its requirements and enquire whether the caller is still interested. The RA will explain the need to collect some information from the caller to determine whether they are eligible to participate and request verbal permission to proceed. A script and screening instrument will be used to standardize this phase of enrollment. Upon obtaining verbal consent the RA will complete the phone screen. A standardized formula will guide the RA to determine whether the caller is (a) eligible, (b) potentially eligible-pending or (c) not eligible.
If the caller has been recruited via options 2 and 3, the RA will request contact information for the participant's physician and obtain verbal permission to send the participant's physician a letter to obtain a confirmation of heart failure diagnosis. Once the confirmation is received, the RA will contact the individual to schedule a screening orientation session. If the physician does not confirm a diagnosis of heart failure, the individual will be called and notified that they are not eligible for the study. Patients signaling interest will be invited for a screening visit.

Screening visit: Once the potential participant has confirmed interest in participating, he/she will receive a consent form to read discussing the purpose of the study, its risks and benefits and clearly stating that he/she can withdraw at any time without any adverse consequences. *This study will involve only ONE informed consent process.* Full informed consent will be obtained in

person by the RA in a private room at the CBPM after a thorough explanation of the study design, of the study intervention, and of the risks and benefits involved. Since the study requires access to protected health information (PHI), HIPAA authorization will be required from each individual in order to access his or her medical records. Signed informed consent forms will be kept in locked filing cabinets separate from all data. Participants will receive a copy of the consent for their records. *Once informed consent procedures are completed*, participants will undergo a battery of screening assessments (described in section 9.2). The RA will complete a screening log checking that all eligibility criteria are met at this point.

Screening failures: Microsoft ACCESS© will be used for tracking all participants who expressed interest in participating and were screened for eligibility. We will collect data from all individuals assessed for eligibility (i.e., individuals who consented but then resulted non-eligible at the completion of the screening process) so that we can provide a complete Consort diagram and description of the recruitment process both for publication purposes and as an indicator of future generalizability of the study. We estimate that our screen failure rates will be ~30%, and that 70% of screened participants will be eligible for this study.

Screening window. We anticipate that the time between the completion of all screening procedures and the beginning of the intervention will not exceed 4 weeks. In case > 4 weeks have lapsed, patients will be re-contacted and re-assessed for eligibility.

Randomization. n/a. This is a pre-post design study. NO randomization is involved.

8.3. Retention plan

Patients will be asked to provide two different telephone numbers (home and mobile phone number) and an email address. The study tracking system will identify participants due for a visit. We will send mail/email reminders or phone messages to remind patients of their follow-up appointments or class sessions. We will also maintain contact by sending birthday and holiday cards. Participants who wish to drop out of the study will be queried as to their reasons for doing so and every attempt will be made to address their concerns. To encourage compliance with assessment visits, we will provide a $ 50 incentive at each visit (baseline, end of intervention, and 6 months - $150 total). *No incentive* will be provided for participation in intervention sessions, as this might bias attendance and threaten the validity of our findings.

9 STUDY DESIGN AND PROCEDURES

9.1. Study Outcomes

Primary outcomes:

1) Feasibility. Key feasibility metrics will include the number of screened, eligible, consented and randomized participants; retention rates; session attendance; and individual mindfulness practice.
2) Acceptability will be assessed using a satisfaction survey.

Secondary outcomes:

1) Pre/post intervention change in self-reported and objectively assessed medication adherence and functional capacity (a clinical marker of medication adherence). Hypothesis: we will observe significant pre-post intervention improvements in medication adherence and functional capacity.
2) Changes in memory and attention change over time and associations between changes in memory and attention and changes in medication adherence. The goal is to explore potential mediating effects that will be formally tested in a future fully powered RCT. We hypothesize that MT will improve working memory, and that such changes will in turn be associated with improvements in adherence. Although measures of memory and attention are our primary posited mediators, we will also explore the role of mindfulness and depressive symptoms (additional potential mediators of MT effect).

9.2. Design Overview

This is a pilot study use a pre-test/post-test design. The overall duration of this study will be 2 years; each individual (n=50) will be involved for 6 months. Assessments will be conducted at baseline, end of treatment, and 6- months after baseline.

9.3. Study Intervention

Intervention setting. Intervention sessions will be individually delivered over the phone. Prior to the beginning of the intervention instructors will contact participants to set up the best time to deliver the intervention.

Session frequency. Participants will receive a 30-minute phone call session once a week for 8 weeks.

Mindfulness training (MT). The intervention protocol is based on the MT protocol pilot-tested in our preliminary work (see Appendix 1 for a script of each session). This intervention maintains the basic components of Mindfulness Based Stress Reduction (MBSR) but has been streamlined to distill the active ingredients for phone delivery. The MT intervention involves training in the following practices: (1) Awareness of breath, a technique in which trainees learn to attend to the sensations associated with breathing; and (2) Body scan, a technique based on the cultivation of attention to bodily sensations that would normally go unnoticed. Later, participants are gradually trained to (3) direct their attention to simple activities of daily life and (4) to become aware of their own thoughts and emotions. Only at the final session they (5) practice "open awareness" – a technique by which the participant is invited to direct his/her attention to any event arising in their field of experience at a given moment, whatever it may be, e.g., a physical sensation, sound, emotion, or thought.

Table 2. Session by Session Overview of the MT Intervention Components

	Session 1	Session 2	Session 3	Session 4	Session 5	Session 6	Session 7	Session 8
Awareness of breath	X	X	X	X	X	X	X	X
Body scan			X	X	X	X	X	X

Awareness of daily experience exercise		X						
Informal practice exercise				X				
Awareness of sounds exercise					X			X
Awareness of emotions exercise						X		X
Awareness of thoughts exercise							X	X
Open awareness								X

Individual home practice. In addition to the weekly training session, participants will practice mindfulness techniques for 20 minutes daily on their own with the guidance of a digitally recorded, standardized guided mindfulness practice containing the techniques learned with the instructor. The mindfulness practice digital recording will be provided in different formats (CD or MP3 file) depending on the participant's preference; CD players will be offered to participants who do not possess one and MP3 versions will be uploaded onto the patient's smartphone or other device. (Please see Appendix for a script of the CD/MP3 recording).

MT instructors. The MT instructors (Szneke, Sharaf, Legro) will be graduates of the teachers' training program at the University of Massachussetts Center for Mindfulness with ≥ 5 years teaching experience who have already participated in studies involving phone-delivered MT. To ensure consistency of delivery, each patient will be trained by the same instructor throughout the intervention. Instructor will receive one 2-hour long training session (review of MT protocol. Fidelity procedures).

9.4. Concomitant Interventions

Allowed Interventions: Participants are allowed to continue ALL the medications and follow all behavioral recommendations prescribed by their care providers (i.e. dietary recommendations).

Prohibited Interventions: Concurrent yoga, tai chi, or other mind-body training.

9.5. Blinding

The RA will be responsible for the day-to-day management of the study and will not be blinded to the exposure status of the participants. We note, however, that study participants will independently perform cognitive tests and enter other data via computer interface with no RA involvement. All personnel responsible for data management and analysis will be blinded to participants' exposure status.

The mindfulness instructors cannot be blinded to exposure status but will be blinded to study hypotheses.

10 STUDY ASSESSMENTS

Screening, baseline and follow-up assessments will be completed in a private room located at the CBPM. The CBPM occupy 20,000 square feet of space in the Coro Building, of which 3700 for the exclusive purpose of meeting with research subjects. This area consists of conference rooms for orientations and group meetings, private assessment rooms for one-on-one appointments, and two control rooms from which an operator can monitor private observation rooms. The CORO Building has 24-hour security including security officers, a panic system to alert security, and any other emergency response system if necessary. We also have several staff certified in CPR and Basic Life Saving response. In response to the COVID-19 pandemic, and due to the fact that this is a high-risk population, follow-up assessments will now be completed over the telephone, via video-conference (using secure, HIPAA compliant videoconferencing software), or by mailing study surveys (that will be returned using pre-stamped envelopes) depending on the participant preference and internet accessibility.
The full assessment package will take approximately 45 minutes to complete. Since not all participants can be reached for assessments on their due date, windows have been established to determine when assessments are counted as missed (table 3).

Table 3.

Assessment	Window before	Window following
3 months	+/-1 week	+/- 1 week
6 months	+/-1 week	+/- 1 week

10.1. Study Assessments Schedule

This table diagrams the study measures and the schedule of administration.

	Screening	**Baseline**	**At each session**	**3 m**	**6 m**
Consent form	X				
HIPAA	X				
Contact information	X				
Eligibility check log	X				
Cognitive impairment (BOMC)	X				
Adherence (Voils scale part 1)		X		X	X
Depression (HADS)	X			X	X
Height, weight, hip, waist measures		X		X	X
Blood pressure		X		X	X
Demographics		X			
Medical history		X			
Medications & other therapies		X		X	X
N screened		X			
N eligible		X			

N refusing to participate		X			
Reasons for refusal		X			
Dropouts and lost to follow-up				X	X
Reason(s) for dropping out				X	X
Sessions attendance			X		
Individual MT practice			X	X	X
Program satisfaction scale				X	X
Program evaluation survey				X	
Sleep Quality (PSQI)		X		X	X
Cognitive assessment battery		X		X	X
Walking test		X		X	X
Social Support		X		X	X
Depression (HADS)		X		X	X
Mindfulness (MAIA)		X		X	X
Five Facets of Mindfulness (FFM)		X		X	X
Adherence (MEMS caps)		X		X	X
Voils Self-Reported Adherence (part 2)		X		X	X

MT = mindfulness training
Note: screening and baseline assessments occur at same visit

10.2. Screening Assessments

These evaluations occur to determine if the candidate is eligible for the study (see also 7.2).

- The Blessed Orientation Memory and Concentration test (BOMC)[79] will be used to screen for ***severe cognitive impairment***. Patients with BOMC scores ≥10 will be excluded because they lack the cognitive skills to learn the intervention.
- ***Depression*** will be assessed using the HADS,[64] a self-administered questionnaire with two sub-scales (0-21) measuring anxiety and depression, with higher scores indicating greater psychological morbidity. A good correlation has been reported between the HADS and other commonly used measures of depression.[65] Finally, the HADS has been validated in cardiac patients;[66,67] since the HADS focuses on cognitive symptoms of depression instead of physical symptoms, it is particularly useful in these patients, where symptoms of the underlying cardiac disease often overlap with the physical symptoms of depression. Scores will be calculated immediately after completion. Patients with HADS scores indicating severe distress (>14) will be excluded from the study and referred to their primary provider – please see Human Subjects section for details.
- We note that in this version of the protocol we eliminated "suboptimal adherence" as an inclusion criterion. The reasons for this modification are as follows: 1) Even if patients report to be adherent at baseline, adherence declines over time. By including only participants who are non-adherent, we would not be capturing those that later become non-adherent. 2) This phenomenon is documented in the HF literature: adherence tends to decline even among HF patients who are initially adherent.[12-14]

10.3. Baseline Assessments

- Medication Event Monitoring Systems (MEMS) will be used as an ***objective measure of medication adherence***. MEMS caps (AARDEX USA, Inc., Union City, CA) are medication containers and caps equipped with a digital microchip recording date and time of each cap opening and are one of the most widely used objective method of adherence assessment in research settings.[36,68-70] We will monitor ONE medication per patient using the criteria adopted by Wu et al.[12] Briefly, if the patient takes any HF medication *twice* a day, this medication will be MEMS-monitored. If all HF medications have the same daily prescription schedule, the β-blocker will be monitored. If the patient does not receive a β-blocker, the ACE inhibitor or the angiotensin receptor blocker will be used instead. If none of these drugs is prescribed, the aldosterone antagonist or statin, or digoxin or diuretic will be monitored.[12] Participants will receive a MEMS bottle at the baseline visit and will be instructed to open it only when they actually take their medication; they will also be trained to keep track of unscheduled lid openings (i.e. refills, accidental openings) in a diary; these events will be removed prior to analysis. After the baseline visit, participants will enter a 30-day run-in for the assessment of baseline adherence. Participants will start using the cap on the day following the baseline visit (=time 0), and the intervention will start 30 days later; this 30-day period will be considered our baseline.
- ***Self-reported medication adherence*** will be measured using the Voils medication adherence measure,[71] a validated measure of adherence behaviors (part 1) as well as reasons for non-adherence (part 2). The item response category consistent with perfect adherence (i.e., "none of the time" or "never") are assigned a value of 1, and the item response category reflecting most nonadherence is assigned a value of 5 (i.e., "all of the time" or "always"). Higher scores indicate worse adherence behaviors.
- ***Cognitive measures*** (selected from the NIH Toolbox Cognition module, see Appendix) will include:
  1) <u>The Flanker Inhibitory Control and Attention Test</u>. This test measures attention and inhibitory control. During the test, participants are instructed to focus on a stimulus while inhibiting attention to another stimulus (arrows). Sometimes the middle stimulus points in the same direction as the "flankers" (congruent) and sometimes in the opposite direction (incongruent) over 20 trials;
  2) <u>The Oral Symbol Digit Test</u> assesses working memory and processing speed. A key with nine abstract symbols is presented - each paired with a number between 1 and 9. Participants are asked to verbally indicate which numbers go with the symbols that are presented in a long string on the computer screen. The participant is given 120 seconds to call out as many numbers that go with the corresponding symbols as he/she can – in order, without skipping any;
  3) <u>The List Sorting Working Memory Test</u> requires working memory for the sequencing of visually and orally presented stimuli. Pictures of foods and animals are displayed with accompanying audio recording and written text (e.g., "elephant"), and the participant is asked to say the items back in size order from smallest to largest, first within a single dimension (either animals or foods) and then on two dimensions (foods, then animals).
  4) <u>The Picture Sequence Memory Test</u> is a measure of episodic memory. Sequences of pictured objects and activities are presented in a particular order. The participants are asked to reproduce the sequence of pictures that is shown on the screen. Participants respond by dragging pictures from the yellow box on the screen into the gray boxes on the screen.

5) The Dimensional Change Card Sort Test is a measure of cognitive flexibility and attention. Two target pictures are presented that vary along two dimensions (e.g., shape and color). Participants are asked to match a series of bivalent test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after a number of trials, according to the other dimension (e.g., shape). The relevant dimension for sorting is indicated by a cue word (e.g., "shape" or "color") that appears on the screen for all participants.

Performance on all these measures correlates significantly with scores on "gold standard" neuropsychological tests of each of the cognitive domains of interest and have high test-retest reliability, internal consistency, and convergent and divergent validity.[72-77] Each test will be independently completed by study participants (3-5 minutes each) after a baseline practice trial using a study tablet. During phase 1 of this study we will develop a standardized protocol for the administration of cognitive tests, which will be included in the study manual of operations. The total time needed for the administration of the cognitive battery is 24 minutes.

- ***Social support***: The Multidimensional Scale of Perceived Social Support is a 12-item, uni-dimensional tool to measure how one perceives their social support system, including individuals sources of social support (i.e., family, friends, and significant other).
- ***Depression*** will be assessed using the HADS,[64] a self-administered questionnaire with two sub-scales (0-21) measuring anxiety and depression, with higher scores indicating greater psychological morbidity. If at any time during the study a participant scores >14 on the depression subscale, the RA will start a suicidality assessment (see suicidality protocol).
- ***Mindfulness*** will be assessed using the Multidimensional Assessment of Interoceptive Awareness (MAIA),[78] a 32-item, 8-subscale self-report measure (recommended by the NIH Science of Behavior Change Research Network), with higher scores indicating higher levels of positive awareness as well as the Five Facets of Mindfulness (FFM),[79] an instrument derived from a factor analysis of questionnaires measuring mindfulness in daily life.
- ***Sleep quality*** will be assessed using the Pittsburgh Sleep Quality Index (PSQI),[80,81] a measure of sleep quality and quantity, based on recall of sleep behaviors in the past month. Scores coded from zero to three; the overall score range is 0-21.
- ***Weight, height, waist/hip ratio*** will be measured using standardized procedures (described in the study manual of operations)
- ***Blood pressure*** will be measured using a Dinamap XL automated BP monitor according to current recommendations.[824]
- ***Exercise capacity*** will be assessed via the 6 min walking test, a simple, safe and reliable first-line assessment of functional status[835] that correlates with peak oxygen uptake[846] and also predicted survival in HF drug trials.[87]
- ***Socio-demographics*** (age, sex, race/ethnicity, education, marital status, income, insurance status) will be self-reported using standard forms validated in other studies
- ***Medical history*** (coronary risk factors; *previous MI or stroke; other co-morbidities)*: this information will be abstracted from medical records using standard abstraction forms that have been validated in previous studies

- ***Medications & other therapies*** information will be self-reported using a standardized form.

10.4. Follow-up Assessments

The following assessments will take place at 3 and 6 months since randomization:

- ***Self-reported adherence behaviors (Voils)***
- ***Objectively assessed adherence***
- ***Cognitive assessment battery***
- ***Social support***
- ***Depression***
- ***Mindfulness*** **(MAIA and FFM)**
- ***Sleep Quality (PSQI)***
- ***Physical capacity (walking test)***
- ***Weight, height, hip and waist measurements***
- ***Blood pressure***
- ***Acceptability***. To assess acceptability we will use the intervention enjoyment scale used in a previous study.[858] We will ask participants to rate the intervention on a scale from 0 to 4.
- ***Attendance*** at classes will be recorded at each session by the instructor using a mindfulness attendance log.
- ***Individual mindfulness practice*** at home will be self-reported by means of a diary to be kept daily. Logs will be collected in person at follow-up visits.
- ***Program evaluation*** will be determined using a standardized form we used in previous studies.

In response to the COVID-19 pandemic, and due to the fact that this is a high-risk population, BP will be self-measured at the planned assessed date and self-reported values will be communicated to the RA over the phone. This will be noted in the Access database and in future manuscripts and scientific reports.

11 DATA COLLECTION

11. 1. Data sources

Data will be collected and using pre-tested and validated forms, which have been found to be acceptable by the type of individuals who will participate in this project. Information about medical history, hospital readmissions or unplanned clinic visits will be collected from electronic medical records or directly from the patient's primary care physician or cardiologist using previously designed abstraction forms. We will develop electronic versions of each study form and data abstraction form for data entry using RedCap technology.

11.2. Data safety

Electronic data will be stored in password protected data files accessible only to authorized project personnel including the Principal Investigator, Data Systems Analyst, Statisticians and SRA. All data files will be automatically backed up daily. Paper data will be stored in locked file cabinets. Data containing identifiers (e.g., name, address, phone number of participants from ACCESS files) will be stored on password-protected secure servers separately from de-identified study data (e.g., surveys, screeners).

11.3. Data collection

The RA will collect data via in-person interviews at each data collection point. In response to the COVID-19 pandemic, and due to the fact that this is a high-risk population, follow-up assessments will now be completed over the telephone, via video-conference (using secure, HIPAA compliant videoconferencing software), or by mailing study surveys (that will be returned using pre-stamped envelopes) depending on the participant preference and internet accessibility. Research Electronic Data capture (REDCap) technology[108] will be used to for direct data entry in electronic CRFs during the interviews; clinical data will be entered by the RA from the abstraction forms into electronic version of the abstraction forms in REDCap. Any ambiguity in the response to a question will be brought to the attention of the Data Systems Analysts for clarification. If the Data Systems Analyst is unsure how to code the response, the matter will be brought to the attention of the PI. The Data Systems Analyst will maintain a log so that future occurrences of problems will be handled in the same manner.

12 DATA MANAGEMENT

12.1. Tracking Systems

Prior to beginning subject recruitment; the Data Systems Analyst will develop a tracking system using Access software. The tracking system is essentially a reminder and participant tracking system to aid the study RA in ensuring that all procedures are followed, treatment are adhered to, and assessments administered in a timely fashion. The tracking system will include all steps included within the Recruitment, Treatment and Follow up phases of subject participation in the trial. Quantitative data will be entered into an Access database where they will be stored for cleaning.

12.2. Data entry and storage

Our major data management and analysis needs for the proposed project can be met by using a Pentium-based microcomputer. The data systems analyst will conduct data management under the supervision of the study biostatistician and the PI. De-identified data will be exported directly through the REDCap interface into study datasets. STATA©10, Statacorp-LP statistical software[72] will be used for statistical analyses.

Electronic data will be stored in password protected data files accessible only to authorized project personnel including the Principal Investigator, Data Systems Analyst, Statisticians and RA. All data files will be automatically backed up daily. Paper data will be stored in locked file cabinets. Data containing identifiers (e.g., name, address, phone number of participants from ACCESS files) will be stored on password-protected secure servers separately from de-identified study data (e.g., surveys, screeners).

The Data Systems Analyst will work with project statistician Dr. Dunsiger and the PI to ensure that data are cleaned prior to analysis. When ready for analysis, he will provide a SAS database of collected data to the statistician.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1. Treatment Fidelity

Assessments of treatment fidelity will be performed following the guidelines developed by the Treatment Fidelity Workgroup.[86] During the start-up period, auditor checklists will be created and used to monitor fidelity to the intervention. Checklists will be reviewed weekly by Dr. Salmoirago-Blotcher who will oversee treatment fidelity procedures. Optimal treatment fidelity would be evidenced by 100% of objectives met. If less than 85% of treatment-specific objectives are met, the auditor will remediate instructor's training as needed.

13.2. Training

Staff involved in data collection will be trained and certified regarding their competence. The RA will receive extensive training in the administration of cognitive tests by Dr. Cohen prior to study inception. This includes training on administration and scoring of all questionnaires as well as on review assessment instruments immediately for omissions. When information is missing or incomplete, the RA will contact participants to obtain the necessary information. *A manual of procedures* will be developed during the study start-up period that explicitly describes the specific procedures related to data collection and quality assurance. At study beginning, the first 10 subjects will have their data audited to make sure there are not any systematic problems with regards to entry. This preliminary audit process will reveal any possible problems at the onset as opposed to the end of the study which would result in more work cleaning the data.

13.3. Data monitoring

Under supervision from the PI and the Biostatistician (Dr. Dunsiger), the Data Systems Analysts (Chris Breault) will ensure that entered data accurately represent data collected. She will conduct error-checking procedures quarterly on all data to ensure their accuracy. Data entry systems developed using Access will include appropriate skip patterns and parameter limits to ensure that data are entered accurately (e.g., item response formats from 1-5 will not permit entry of other numbers). Data entry systems will be tested to ensure that these constraints are working correctly prior to entering real data. REDCap employs automatic checks for values that are out of range or represent errors of logic. Outliers will be corrected if possible with verification from participants.

Quantitative data will be cleaned prior to analysis and then made available to the study statisticians for analysis. Dr. Dunsiger will be primarily responsible for the final outcome analyses and will assist in the preparation of manuscripts and reports.

13.4. Metrics

All data designated as primary outcome data will be subject to a 100% cross-referencing with the original paper copy. This audit must have an error rate less than 1%. If the verification fails the audit, all data will be re-entered, the original computer files discarded, and the newly re-entered data audited. This process will continue until the audit no longer exceeds the maximum allowable error rate. All audits will be supervised and documented by the study's Data Systems Analyst.

All other entered information (non-primary outcome data) will be subject to a 20% sample that will be cross-referenced with the original paper copy. This audit must have an error rate less than 1%. If the sample fails the audit, all data will be verified against the paper originals. If the error rate of the complete audit is greater than 1% then all data will be re-entered, the original computer files discarded, and the newly re-entered data audited. This process will continue until the audit no longer exceeds the maximum allowable error rate. At the discretion of the study's Principal Investigator, the full audit may be omitted in favor of a complete re-entry of the original paper data. All audits will be supervised and documented by the study's Data Systems Analyst.

14 STATISTICAL CONSIDERATIONS

14.1. Preliminary analyses

Preliminary analyses will examine comparability of participants at baseline on demographic and other characteristics using Fisher or t-tests depending on the specific variable characteristics (categorical or continuous). We will examine the distributional properties of continuous variables to determine if normalizing transformations should be applied before conducting further analyses. If group differences are found for any variables, we will evaluate them and statistically control them in outcome analyses (e.g., employing them as covariates in linear or logistic regression analyses to control for their effects on the outcomes). After all the data have been collected, and before conducting the final outcome analyses, we will explore the relationship of several key variables that could impact the outcome, such as participant attendance and number of study contacts during the study. If there are group differences on these variables and/or there are relationships of these variables to the outcomes, we will include them as covariates in our analyses.

14.2. Primary Outcomes: feasibility and acceptability

We will calculate retention and attendance rates as well as program satisfaction scores at 3 and 6 months.

Feasibility. We will consider either dose feasible under the following conditions:
If we achieve study retention rates of 80% at the last FU visit
If patients attend at least 70% of the planned classes
If patients report to have completed 70% of the assigned individual home practice exercises

Acceptability. A dose will be considered acceptable if at least 80% of participants will indicate grade 4 enjoyment ratings on a visual scale from 0 to 4 (4=high enjoyment; 0=no enjoyment).[858]

14.3. Secondary Outcomes

To obtain effects of MT on adherence and functional capacity, we will use a series of generalized linear models (GLMs), in which secondary outcome measures will be regressed on time, baseline value of the outcome and potential confounders (i.e., gender, disease severity, social support). Standardized estimates will allow for comparison across different measures of adherence. GLMs

allow for a flexible group of outcome distributions (e.g., binary, continuous); model specification includes determining the distribution and appropriate link function. We will use GLMs to explore changes over time in potential mediators (cognitive function, mindfulness and depressive symptoms) and, in a separate set of models, whether changes in these constructs are associated with changes in secondary outcome variables (adherence and functional capacity). Interest is in gaining estimates of effect for both of these potential pathways. We will also assess potential moderating effects of baseline levels of adherence on our adherence outcomes.

14.4. Sample Size Considerations

We aimed to obtain 80% power to detect a significant change over time in secondary outcome measures and potential mediators. Consistent with expert opinion,[90,91] we integrated several sources of evidence to determine an expected effect size for power calculations. We based our estimates on (a) correlations between mindfulness and self-reported adherence from our prior work (see C.1) (rho=0.68, $p<0.01$),[44] (b) results from an observational study showing association between lapses in attention and adherence (OR=2.65, $p=0.02$)[22] and (c) a longitudinal study (n=309) among HF outpatients showing associations between memory and medication adherence (beta=0.51, $p<0.01$).[26] With n = 50 and two-sided $\alpha=0.05$ we will have 80% power to detect significant effects of MT on adherence, functional capacity, and mediator pathways (changes over time in mediators and their association with outcomes).

14.5. Missing data

Analysis will be performed according to the intention to treat approach. Withdrawals will be asked to complete follow-up assessments and home visits or phone interviews will be arranged if necessary. If we encounter substantial missing data, possible options will include using accepted statistical methods (e.g., use of complete data only, use of multiple imputation, use of modified weights and model-based procedures). Sensitivity analyses will be conducted using different assumptions regarding the mechanism of missingness.

15 REGULATORY REQUIREMENTS

15.1 Institutional Review Board (IRB) Review

This protocol and any subsequent modifications will be reviewed and approved by the IRB, which is responsible for oversight of the study. The consent form and HIPAA forms are attached to the IRB submission.

15.2 Informed Consent and HIPAA

Consent will be obtained at one time point during this study (at screening visit 1).
1) Individuals interested the study will be screened by the study RA in a phone conversation to determine initial eligibility. The RA will briefly describe the study and its requirements and enquire whether the caller is still interested. If the caller is still interested, the RA will explain the need to

collect some preliminary information from the caller in order to determine whether they are eligible to participate. A script and screening instrument will be used to standardize this phase of enrollment. 2) Individuals who meet the initial eligibility criteria and who are interested in participating will provide written consent using an IRB approved consent form and HIPAA authorization form. In addition to describing the study and the participant's involvement in detail, the consent form also emphasizes that participation is voluntary, that consent may be withdrawn at any time, and that participants may withdraw from the study verbally or in writing by contacting the study RA and/or the Principal Investigator. Participants are given ample opportunity to ask questions before providing consent. Contact information for the RA and PI, as well as the IRB (for complaints) is provided in the consent form. Signed informed consent forms and HIPAA forms will be kept in locked filing cabinets separate from all data. Participants will receive a copy of the consent and HIPAA document for their records.

15.3 Subject Confidentiality

Protection of Subject Privacy: All phone contacts with the participants will take place in a private, locked office and will be conducted by a trained RA who has been trained and certified in the protection of human subjects in research trials and HIPAA requirements according to TMH policies. Individuals who are interested in the study will provide Contact Information (e.g., name, address, phone, email) and will be scheduled for a screening visit (screening visit 1) n orientation visit to learn more about the study requirements and procedures, and to sign written informed consent as approved by TMH Institutional Review Board (IRB).

Data safety

- Subjects will be identified with a randomly generated identification code unique to the subject and all personal identifiers will be removed from the study questionnaires and from datasets. Electronic communication with outside collaborators will involve only unidentifiable information. AE reports and annual summaries will not include subject-identifiable material.
- Data collected for screening (i.e. reasons for ineligibility and refusal) and tracking reasons (Access data base) that contain identifiers will be stored into a password-protected server separate from other study data and will be destroyed at study completion. This Access database is password accessible only to the study SRA, the data systems analyst, and the PI.
- Signed HIPAA forms and consent forms will be stored in locked filing cabinets separate from all other study data.
- Patients will be informed in the consent form that MT sessions will be digitally recorded for assessments of treatment fidelity and digital recordings will be treated as explained above for focus groups recordings.
- All copies of de-identified study questionnaires (paper and/or electronic) will be destroyed at the earlier of two dates: 1) seven years after the end of the study; 2) after the manuscript based on the work is published.

15.4. Study Discontinuation

The study may be discontinued at any time by the IRB as part of their duties to ensure that research participants are protected.

15.5. Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in the guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in order to protect the safety, welfare, or rights of subjects or others.

Unexpected, serious and intervention-related SAEs will be immediately (< 24 hours) reported to the chair of the IMC and the IRB in accordance with requirements.
Participants will be asked about all AEs at each intervention session and at each follow up assessment. AEs will be recorded on the AE log and noted on the CO form. Procedures for handling the reporting of AEs and SAEs to the IRB and the IMC are detailed in the DSM plan (section 6).

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