MBCT Via Group Videoconferencing for Acute Coronary Syndrome Patients With Depressive Symptoms: A Pilot RCT

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I. BACKGROUND AND SIGNIFICANCE

a. Historical Background

It is critical to treat depression in patients with acute coronary syndrome (ACS). Among the one million ACS patients in the U.S. each year (e.g., myocardial infarction, unstable angina), up to 45% have elevated depression symptoms. Even mild elevations in depression symptoms double the risk of mortality after ACS. Meta-analyses of over 4,000 ACS patients and 53 studies have found that depression is an independent risk factor for recurrent cardiac events, re-hospitalizations, cardiac mortality, and all-cause mortality, beyond other traditional risk factors. Left untreated, depression persists for years and doubles the risk of death through biological and behavioral mechanisms. Biologically, depression causes inflammation through neuroendocrine alterations, leading to atherosclerotic plaque formation and rupture. Behaviorally, ACS patients need to make multiple lifestyle changes, but depression symptoms (e.g., disinterest, lack of motivation) prevent engagement in cardiac health behaviors (e.g., physical activity, diet). Thus, depression treatment is necessary to promote biological and behavioral changes important for survival.

Depression treatments for ACS patients need improvement. More ACS patients prefer psychological (75%) rather than pharmacological depression treatments (20%). However, the recommended psychological intervention, cognitive-behavioral therapy (CBT), has limited effects on depression and cardiac outcomes. Targeting the mechanisms that link depression to ACS could improve treatment efficacy, but CBT does not aim to target a key mechanism, i.e., inflammation. Consistent evidence from multiple meta-analyses suggests that depression is associated with elevated levels of inflammatory cytokines, particularly C-reactive protein (CRP), interleukin-6 (IL-6), and TNF-α. These same specific cytokines are also elevated, positively correlated with depression symptoms, and independently increase the risk of mortality in patients with cardiac disease. Of note for depression treatment, the relationships are bidirectional: treating depression reduces inflammation, but reducing inflammation also reduces depression symptoms, making CRP, IL-6, and TNF-α salient treatment targets for both depression and cardiac health in ACS patients.

Mindfulness-Based Cognitive Therapy (MBCT) could improve depression and cardiac health for ACS patients. MBCT is an 8-week manualized group intervention that combines CBT with mindfulness meditation to treat depression; it is as effective as antidepressant medication for relapse prevention and reduces symptoms in active depression. The American Heart Association (AHA) recently highlighted the potential benefits of meditation for cardiac health and the need for

further research in this area. Indeed, through the addition of mindfulness training, MBCT could improve both depression and cardiac health. First, mindfulness meditation can reduce levels of CRP, IL-6, and TNF-α, which reduces depression symptoms and benefits cardiac health. Second, meditation increases pro-sociality (e.g., compassion, altruism) and social support, both of which reduce depression symptoms. Given that social isolation is an independent risk factor for ACS mortality and pro-sociality improves cardiovascular functioning, social improvements could have direct benefits on cardiac health. Next, MBCT improves emotion regulation (e.g., rumination about a recurrent event, acceptance of lifestyle changes), which is a key treatment target for depression. Lastly, mindfulness training improves cardiac health behaviors, likely by improving emotional outcomes. Improvements in depression also lead to further improvements in inflammation and pro-sociality to further promote cardiac health.

b. Previous pre-clinical or clinical studies leading up to and supporting the proposed research

Research supports the feasibility of MBCT for depression treatment in ACS patients. Two meta-analyses (18 trials) have demonstrated that mindfulness interventions are feasible, acceptable, and reduce depression symptoms in patients with cardiovascular disease (d = .35 - .61). ACS patients are similar to other cardiac disease patients (e.g., age, comorbidities) and thus are also likely to find mindfulness interventions acceptable. In fact, ACS patients may be most interested in depression treatment because they are motivated to improve their health following the acute cardiac event. Most research in patients with cardiovascular disease has used Mindfulness-Based Stress Reduction (MBSR), which is very similar to MBCT, but does not incorporate a CBT approach to target depression specifically. MBCT shows larger effect sizes for depression than MBSR and thus might be particularly useful for ACS depression treatment.

An electronic health (e-health) approach is needed to improve treatment outreach. Most ACS patients prefer behavioral depression treatments, but these are burdensome, not widely accessible, and present barriers. In a study of nearly 700 primary care patients, 78% of those with depression reported logistical and emotional/physical barriers to accessing treatment. E-health technologies can overcome these barriers to reach more patients and effectively treat depression. In a study of over 200 patients with cardiovascular disease, 85% had internet access and 74% of them preferred e-health interventions. ACS patients tend to be older adults ($\geq$65 years), the fastest growing group of computer and internet users, who report positive experiences with technology used at home. A systematic review of 54 trials found that e-health interventions are feasible for older adults with medical problems, including those with cardiovascular disease.

It is feasible to deliver MBCT via e-health technologies. E-health mindfulness interventions are feasible and can improve health outcomes in patients with medical problems. However, research has focused on websites that patients use independently, which does not allow for synchronous contact with a clinician or peers, leading to a smaller treatment effect and increased attrition, and eliminating the health benefits of social support. Group videoconferencing combines accessibility with synchronous contact, shows comparable efficacy with in-person treatments, and is a validated approach to behavioral intervention delivery. Two studies demonstrated the feasibility of videoconferencing to deliver mindfulness interventions to patients at their own home. Thus, group videoconferencing is a promising but underutilized approach to MBCT delivery.

MBCT via group videoconferencing is likely to be attractive and feasible for ACS patients. Web-based mindfulness interventions are feasible and reduce depression symptoms in patients with cardiovascular disease and other older adult populations. The AHA has emphasized that a benefit of meditation for cardiac health is the possibility of online delivery, but no research has applied MBCT via group videoconferencing to ACS patients with elevated depression symptoms.

Our preliminary work supports the use of virtual MBCT for ACS patients. We recently conducted a qualitative study (individual patient interviews) to solicit patient's perspectives and needs for a behavioral depression treatment based on MBCT (IRB Protocol Number 2018P001000). Patients were open and interested in a mindfulness program, identified a range of symptoms and needs for the intervention to target, offered suggestions for promoting videoconferencing feasibility, and expressed openness to participate in dried blood spot research procedures. We developed an adapted MBCT protocol based on this feedback, which we recently tested in an open pilot trial of n=7 patients with ACS and depressive symptoms (IRB Protocol Number 2020P000045). Those who completed the intervention (n=4) reported high ratings of intervention acceptability, videoconference acceptability, comfort with the dried blood spot procedures, and improvements in depression and anxiety symptoms.

c. Rationale behind the proposed research and potential benefits to patients and/or society

The rationale behind the proposed research is that the high comorbidity between depression and cardiovascular disease reflects a complex, mind-body interaction that must be treated using a comprehensive mind-body approach. Mindfulness-based cognitive therapy is an evidence-based intervention with efficacy to treat depression, and improve quality of life in patients with cardiovascular disease. However, this is the first research to adapt MBCT specifically to the needs of patients with depression after an acute cardiac event, test the efficacy of this intervention an randomized trial with an active control group. The potential

benefits to patients in the trial include peer support, attention from a trained clinician, and learning information and skills to improve mood, coping, cardiac health, and quality of life. Given that cardiovascular disease is the leading cause of death worldwide, and the substantial added burden of co-occurring depression and cardiovascular disease, the proposed research has the potential to identify a novel, efficacious, and scalable intervention to improve public health.

II. SPECIFIC AIMS

a. Aim 1: To establish, in a pilot RCT (approx. N=50 participants) with a time- and attention-matched health enhancement control, (a) the feasibility of the recruitment procedures (screening, eligibility, enrollment rates), and feasibility and acceptability of the (b) MBCT and control interventions (adherence, retention, fidelity, satisfaction, group videoconferencing delivery) and (c) data collection procedures by group (adherence, satisfaction). Hypothesis 1a: Recruitment will be feasible as evidenced by screening, eligibility, and enrollment rates; (1b) the MBCT and control interventions and (1c) data collection procedures in both groups will be feasible and acceptable.

b. Aim 2 (exploratory): To explore within-group changes in psychosocial and physical health outcomes following virtual MBCT and the control intervention (e.g., depression, inflammation, emotion regulation, pro-sociality, and health behaviors).

III. SUBJECT SELECTION

a. Inclusion/exclusion criteria

Inclusion criteria:

1. Lifetime ACS per medical record and/or patient confirmation
2. Current elevated depression symptoms (PHQ-9$\geq$5)
3. Age 35-85 years
4. Access to high-speed internet
5. Massachusetts General Brigham patient

Exclusion criteria:

1. Active suicidal ideation or past-year psychiatric hospitalization (per patient report and/or medical record review)
2. Non-English-speaking
3. Cognitive impairments preventing informed consent per medical record review and/or cognitive Screen $\leq$ 4
4. Patient deemed unable to complete the study protocol or has a condition that would likely interfere with the study
5. Is not a Massachusetts General Brigham patient

b. Source of subjects and recruitment methods

Study staff will engage in multiple recruitment modalities to obtain a diverse sample of study participants.

First, patients will be recruited through the RPDR. We will include patients who have and have not agreed to participate in RODY (Research Options Direct to You).

"RODY No" patients identified from the RPDR will be sent a combined opt-out letter from a member of their healthcare team (e.g., cardiologist, primary care provider, nurse practitioner, etc.) and the study team. This letter will be sent via paper mail or Patient Gateway. This letter will describe the study procedures and ask patients to contact the study team within 2 weeks if they would not like to be contacted to hear more about the study. Patients will have the option to opt-out via phone or email. Those who do not opt-out will be contacted via phone by the PI or a trained and CITI-certified research staff member. Patients will be read a brief phone script (attached) informing them of the purpose of the call and asking if they would like to hear more about the research study. Those who agree will undergo eligibility screening (attached). Those who are eligible and interested will undergo informed consent, described below.

"RODY Yes" patients will receive an opt-out letter from the study team (attached). All other recruitment procedures will be the same as for "RODY No".

Only the Principal Investigator and trained research staff will identify and contact patients. Up to approximately 3 calls will be made to a given patient before assuming the patient is not interested and no longer attempting to contact them.

Second, patients will be recruited through hospital flyers (e.g., inpatient/outpatient cardiology clinics, psychiatry clinics). Advertisements will ask patients to contact study staff if they are interested in learning more about the study. In situations where a briefer ad is more feasible (e.g. virtual postings on iPads and computer screens in clinic waiting rooms), a shortened version of the flyer will be posted. The flyers are included in the IRB submission. Specific phone numbers on the flyers will be filled in based on the contact information for the current RA. Phone screening and consenting procedures will be the same as described above.

Third, patients will be recruited via direct referrals from their providers (e.g., cardiologists, psychiatrists). We will inform providers about the study (e.g., via short presentations at their team meetings) and provide them with flyers. Providers may either obtain verbal permission from the patient to share their name and contact information with study staff, or they may provide patients with the flyer to contact study staff on their own. The outreach and phone screening procedures will be the same as described above.

Fourth, patients will be recruited from inpatient cardiac units within MGH. Study staff will review inpatient censuses from MGH cardiac units and/or participate with invitation in inpatient cardiology rounds to identify patients whose available admission information (e.g., laboratory studies) suggests ACS. Study staff will ask the clinical team to confirm the cardiac diagnosis and inquire with the patient whether the patient is willing to hear about an optional study. For willing patients, study staff will discuss the study with the patient and assess for additional study criteria using the same screening procedures described above (e.g., PHQ-9 administration). For patients who screen out or decline assessments, we will retain no personal information. Patients who are interested in hearing about the study and completing the screener, but do not want to do so during their hospitalization, will be given the option to be contacted by phone after their discharge. The same screening procedures would be done by phone at that time.

Fifth, research staff will use EPIC to assist in recruitment. To this end, we have worked with the Partners eCare Research Core (PeRC) to set up the necessary steps. PeRC leverages the Epic EHR to assist researchers in identifying and recruiting patients for their research studies conducted at Partners HealthCare. PeRC will put together a report through EPIC based on a list of predetermined variables (please see attached list of variables to be extracted). After Epic training, and hands-on guidance from the PeRC team, study staff will run this automated report within Epic to identify potentially eligible ACS patients. Study staff will review patients' charts to confirm potential eligibility as needed (e.g., confirm admission diagnoses). Study staff will send patients the same opt-out letters described above via paper mail or Patient Gateway according to RODY status, and the outreach and screening procedures will be the same.

In addition, the PI or trained RA will view Epic patient lists for cardiac units (e.g., Ellison 10, Ellison 11) to identify patients admitted for ACS. Patients' charts will be reviewed to determine if they are RODY or non-RODY patients. RODY patients will receive a phone call or opt-out letter inviting them to participate in the study. For non-RODY patients, study staff will obtain permission from a member of the patient's healthcare team to send a combined opt-out letter from the provider and study team.

Sixth, patients will be recruited through the study's MGB Rally page. Research staff will publish an informational Rally page to advertise the study to MGB patients. Patients will be able to contact study staff if they are interested in learning more about the study. Specific phone numbers on the Rally page will be filled in based on the contact information for the current RA. Phone screening and consenting procedures will be the same as described above.

IV. SUBJECT ENROLLMENT

a. Methods of enrollment, including procedures for patient registration and or randomization

Study staff will approach patients about participating in the study using one the modalities discussed in section III.b. For patients who are not interested in participation, study staff will discontinue contact. For patients who are interested in participation, study staff will screen patients for eligibility (criteria detailed in section III.a). If a patient screens as eligible, they will be asked to provide informed consent using one of the procedures detailed in section IV.b. Following informed consent patients will be 1:1 randomized (see section IV.c) and enrolled in the study using a random number generator.

b. Procedures for obtaining informed consent

A member of the study staff will determine patients' eligibility status, explain the purpose of the study and study procedures, and answer any questions prior to completing informed consent per the information below.

Patients will be provided with the informed consent document electronically or via paper mail. The informed consent document will be carefully reviewed with study staff via discussion with the patient either by phone or videoconference. Patients who are recruited while inpatient may also have the option to complete consent in person. The consent form will include a description of all study procedures and information about potential risks and benefits of participation. It will state that participation is voluntary, that participants can refuse to answer questions that make them uncomfortable, that participants can discontinue participation at any time, and that not completing the study will not compromise their medical care. Special attention will be given during the consent process to the implications of the study design (e.g., randomization) and of receiving an intervention or educational information online via videoconferencing services. Subjects will be explicitly informed that videoconferencing services provide secure HIPAA-compliant videoconferencing software. We will explain to participants that although we will do our best to ensure confidentiality on our end, there is still a potential risk of loss of confidentiality. Participants will also be advised to wear headphones and sit in a quiet place to protect their own, and other group members' privacy.

After the form is reviewed and all of the patient's questions have been answered, the patient may then sign and submit the form electronically or via paper mail. All patients will be provided with study staff contact information if any questions or concerns regarding the research arise.

As stated above, member of the study staff will obtain informed consent in one of three ways, depending on patient preference: 1) electronically (via REDCap or emailed pdf of the consent form), 2) via paper mail correspondence, or 3) in

person (for patients who are recruited while inpatient). Participants who opt to receive the consent materials via paper mail will be asked to provide a mailing address. Participants who opt for electronic consent will be made aware of security concerns related to email communication (as described earlier) and, after specifying their preference for encrypted or unencrypted email, be emailed the informed consent portal via REDCap or electronic copy of the consent form.

REDCap Electronic Informed Consent Process (EIC):
Participants who choose to complete the consent form electronically will be emailed a link for the informed consent portal via REDCap. The REDCap link will connect the participant to an encrypted REDCap portal; the Electronic/Paperless Consent Template Project will be used. Once the participant confirms receipt of the EIC form link, they will be prompted to enter in their full name and birthday to access the informed consent form and verify their identify. This portal will have the electronic (paperless) consent form, exactly identical in content to the paper version, to guide the participant through the consent discussion with study staff over the phone. The participant will be given ample opportunity to ask questions and take their time to consider their participation. If a participant would prefer, they may return to the EIC portal as many times as they would like to review the consent form on their own time. When ready to sign consent, participants will digitally sign and date/time the consent form. Additionally, the participant will be prompted after signing to indicate the method through which they would like to receive a copy of the consent form for their record: digitally or through hard copy. If a participant would like to receive a copy of the consent form digitally, they will be asked their preference to receive the email as encrypted, the default, or opt-out and receive the email unencrypted. These options allow participants to be informed of what an encrypted (Send Secure) email would appear as in their inbox and the steps to get into the email, or alternatively, to give permission to receive the email without this extra layer of security but in a more accessible format. Partner's Healthcare language concerning the Send Secure feature is included to assist in this decision. Study staff will confirm receipt of the digital signature and will sign and date the consent form as the consenting study staff member. At any point, if a participant would prefer to receive a hard copy of the consent form, the EIC process will stop, and study staff will commence the phone and mail correspondence process for informed consent.

Paper Mail Correspondence
Participants may also elect to receive an electronic copy (pdf) of the consent form via email, according to the email security procedures previously described. In this case the participant could print and sign the form and either scan/email or send via paper mail back to the research team.

If the participant would prefer to complete the informed consent process via paper mail, study staff will start by facilitating the informed consent discussion over the phone. Once all questions are answered to the satisfaction of the participant, study staff will mail 2 signed copies of the informed consent form for the participant to review, sign and mail back one copy at their convenience. Participants will be provided with a pre-stamped, pre-addressed envelope for their return. Study staff will maintain one copy of the informed consent form for study records, participants will be instructed to maintain one copy for personal reference.

In-person Informed Consent Process
Study staff will go through the informed consent discussion in a hospital or private room to protect patient confidentiality and answer any questions. Upon consent, study staff will maintain one copy of the informed consent form for study records, and participants will be instructed to maintain one copy for personal reference. Patients who would like more time to consider participation are able to take the forms home with them to review, and if interested, they may complete the consent process electronically or proceed to mail back the consent forms.

Following consent, the participant will be asked to provide and clarify their preferred contact modalities for their participant throughout the study. They will be informed that they can change these preferences at any time. Study staff will document the outcome of this conversation and proceed with participant contact accordingly.

c. Treatment assignment and randomization

Participants will be randomized to a MBCT or a time- and attention-matched health enhancement control in a 1:1 design using a random number generator.

V. STUDY PROCEDURES

a. Study visits and parameters to be measured

Adapted MBCT intervention
The MBCT intervention is based on Mindfulness-Based Cognitive Therapy (MBCT), an evidence-based, manualized protocol for treating depression symptoms. We have developed an adapted MBCT protocol based on our preliminary qualitative work and open pilot trial and continue to make iterative refinements based on patient feedback. Participants randomized to the MBCT intervention will be expected to participate in 8-weekly virtual sessions, in conjunction with approximately 30 minutes of at-home daily practice. Each weekly virtual session will last approximately 1.5 hours. A licensed mental health provider (e.g., LICSW, PhD) trained in the MBCT protocol will deliver the

intervention. The interventionist will receive ongoing supervision and feedback from the PI or MBCT mentor. The MBCT intervention will not be delivered clinically; it is a psycho-educational intervention. We will also send audio recordings used for home mindfulness practice via Partners email (send secure or unencrypted if the patient prefers).

Health Enhancement Control Group

The control intervention will be a group videoconferencing program focused on depression and cardiac health education (e.g., relationship between depression and cardiac health, cardiac risk factors, cardiac health behaviors, finding resources for mental health care). It will follow the same structure as MBCT but will not contain mindfulness practices or psychoeducation. Participants randomized to the health enhancement control group will be expected to participate in 8-weekly virtual sessions, where each session will last approximately 1.5 hours. To promote equivalent between-session practice, participants will identify health behavior goals to work on and track over the week. A licensed clinician or pre-doctoral or post-doctoral fellow with supervision from a licensed clinician will lead the control group.

Data collection

For both the intervention group and control group study assessments include a battery of self-report surveys administered at baseline, post-intervention, and 3-month follow-up; session satisfaction surveys administered after each intervention session; post-intervention individual exit interviews (conducted via telephone or videoconference); blood spot samples self-collected by participants at baseline, post-intervention, and 3-month follow-up (submitted to the research team via paper mail). The intervention group will complete home practice logs submitted between each intervention session. Surveys and home practice logs may be completed via REDCap, email, paper mail, phone, or videoconferencing depending on patients' preferences. Data collection will also consist of viewing and extracting data from the EHR to assess medical and demographic variables (e.g. medical diagnoses, medications, cardiac rehab attendance) and/or confirm eligibility. REDCap is a secure online data collection system.

Survey measures

The self-report survey measures will be the same for the MBCT and control groups. The surveys will be administered within approximately 1-2 weeks before and after the intervention and at 3 months post-intervention. This battery will include the following validated self-report surveys: Assessment of Survivor Concerns (fear of recurrence), CAMS-R (mindfulness), Cardiac History and Symptoms, Current Experiences Scale (CES; resiliency), COVID items,

demographic questionnaire, Expectancy Questionnaire, Experiences Questionnaire (decentering), Group cohesion scale, Hospital Anxiety and Depression Scale (HADS; depression and anxiety), Interpersonal Reactivity Index (IRI; empathy), MAIA-2 body subscales (interoception), MBCT-AS Checklist (fidelity checklist), PHQ-9 (depression), Medical Outcomes Study – Specific Adherence Scale (MOS-SAS; health behaviors), one item from the Short Form-12 (SF-12), Self-Other Four Immeasurables (SOFI; self and other compassion), PROMIS Physical Function (PROMIS-PF; physical function), and The Positive and Negative Affect Schedule-Positive Affect (PANAS-PA). The post-intervention survey will also include a group cohesiveness measures to assess perceived connection with other group members as well as intervention satisfaction questions to assess acceptability. The 3-month follow-up survey will include questions about continued mindfulness practice. The baseline survey, post-intervention survey and post-intervention survey will all include questions related to COVID-19. All three survey batteries are included in the IRB submission.

Post-session surveys

Both intervention and control group participants will receive post-session surveys. The post-session surveys will be administered immediately after each of the 8-sessions and will assess participants' perceptions, and likes and dislikes, of specific intervention or control group components. The post-session surveys for both the control and intervention group are included in the IRB submission.

Home practice logs

Only the intervention group will receive weekly home practice logs. Prior to each session participants will be asked to email, mail, or complete via REDCap a record of their at-home mindfulness practice since the previous session. The home practice logs are included in the IRB submission.

Exit interview

Upon completion of the intervention, participants from both the intervention and control group will be asked to complete a 30-60-minute exit interview via phone or videoconference. These interviews will be audio- and/or video-recorded for transcription.

Dried blood spots

Both intervention and control group participants will be asked to provide dried blood spot samples. Within one week before and after the intervention and 3-months-post intervention, participants will be asked to provide self-collected whole dried blood spots to assess IL-6, CRP, and TNF-α.

b. Drugs to be used

There will be no drugs used in this study.

c. Devices to be used

There will be no devices used in this study.

d. Procedures/surgical interventions

At baseline, post-intervention, and 3 months following the end of the intervention, participants will be asked to complete a dried blood spot sample collection using a minimally invasive finger skin prick technique, which involves pricking the finger with a lancet, milking the finger to produce 5-10 drops of blood onto filter paper, allowing the blood spots to dry, and mailing it to the study team at MGH in a secure envelope. Prior to the start of the intervention, an RA will guide the participant in self-collecting blood samples via a videoconference call or phone call (per the participant's preference). Participants will also be sent written instructional handouts. The RA will ask the participant a series of questions to gauge understanding, provide corrective feedback, and answer any questions the participant might have before proceeding to guide the participant in the procedure.

Participants will be asked to allow the sample to dry overnight, document the date the sample was taken on the filter paper, and mail it to the study team at MGH the next morning. Samples will be received by the RA, who will mark the date of receipt in the study database. Samples can be in ambient air for up to 2 weeks without degradation. We will ask participants to mail the samples within 24 hours of taking them to minimize the time samples are in ambient air. If samples are received beyond 2 weeks of the date indicated on the filter paper, we will ask participants to provide another sample, and participants will be made aware of this possibility in the consent form. Once received, the RA will bring the samples to be stored in a -20°C freezer in the MGH Clinical Research Center lab or mail them to our collaborator at the Laboratory for Human Biology Research at Northwestern University for storage and processing. Blood spots can be frozen at this temperature for several years without degradation.

When initially mailing the blood spot kit to participants, the RA will indicate the participant's study ID number, group assignment, date, and data collection timepoint on the filter paper. Participants will be informed not to write any personally identifying information on the filter paper. This will keep the blood samples de-identified.

Collecting whole blood spots with filter paper has been used in hospitals for decades to collect blood from newborns, and it has proven to be a safe and effective means for collecting and transporting samples in several large NIH-funded field-based studies. The Centers for Disease Control and Prevention have maintained independent quality control efforts and have reported that these

approaches can achieve the same level precision and reproducibility of standard blood collection methods. Our collaborators at Northwestern University have pioneered this technique as leaders in the development, validation and application of whole dried blood spots as a convenient means for collecting, transporting, and processing blood samples from community settings and mind-body intervention research including clinical trials. We used these methods in our recent open pilot trial and found promising feasibility and acceptability in this population (IRB Protocol Number 2020P000045). The dried blood spot samples will be collected using a commercially available, FDA approved Whatman™ 903 Proteinsaver cards and BD Microtainer® Contact-Activated Lancets (gauge 14, incision depth 2mm (8/10”). The samples will not undergo CLIA tests and will be stored for approximately 1-2 years.

There will be no surgical interventions for this study.

e. Data to be collected and when the data is to be collected

The self-report survey measures will be the same for the MBCT and control groups. The surveys will be administered within approximately 1-2 weeks before and after the intervention and at 3 months post-intervention. This battery will include the following validated self-report surveys: Assessment of Survivor Concerns (fear of recurrence), CAMS-R (mindfulness), Cardiac History and Symptoms, Current Experiences Scale (CES; resiliency), COVID items, demographic questionnaire, Expectancy Questionnaire, Experiences Questionnaire (decentering), Group cohesion scale, Hospital Anxiety and Depression Scale (HADS; depression and anxiety), Interpersonal Reactivity Index (IRI; empathy), MAIA-2 body subscales (interoception), MBCT-AS Checklist (fidelity checklist), PHQ-9 (depression), Medical Outcomes Study – Specific Adherence Scale (MOS-SAS; health behaviors), one item from the Short Form-12 (SF-12), Self-Other Four Immeasurables (SOFI; self and other compassion), PROMIS Physical Function (PROMIS-PF; physical function), and The Positive and Negative Affect Schedule-Positive Affect (PANAS-PA). The post-intervention survey will also include a group cohesiveness measures to assess perceived connection with other group members as well as intervention satisfaction questions to assess acceptability. The 3-month follow-up survey will include questions about continued mindfulness practice. The baseline survey, post-intervention survey and post-intervention survey will all include questions related to COVID-19. All three survey batteries are included in the IRB submission.

At the end of each session all participations will complete a post-session survey assessing session likes and dislikes. Between each session intervention participants will be asked to complete home practice logs documenting the frequency of and the thoughts related to their weekly mindfulness practice.

Upon completion of the intervention, participants from both the intervention and control group will be asked to complete a 30-60-minute exit interview via phone or videoconference.

Both intervention and control group participants will be asked to provide dried blood spot samples within one week before and after the intervention and 3-months-post intervention. Samples will be used to examine IL-6, CRP, and TNF-α levels.

Data collection will also consist of viewing and extracting data from the EHR to assess medical and demographic variables (e.g. medical diagnoses, medications, cardiac rehab attendance) and/or confirm eligibility. REDCap is a secure online data collection system.

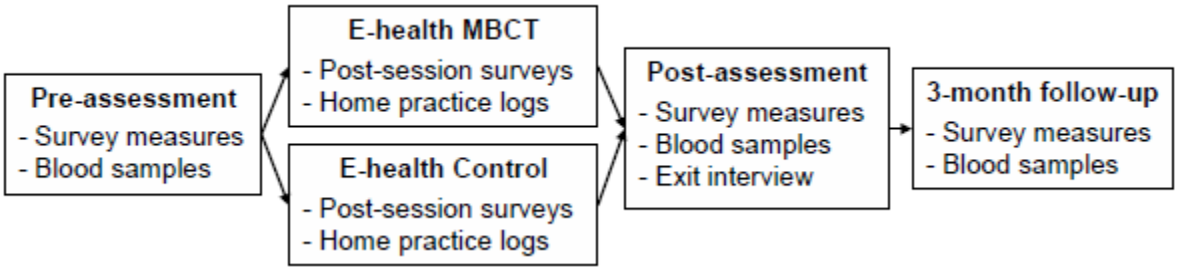

Figure 1. Overview of pilot RCT data collection procedures

VI. BIOSTATISTICAL ANALYSIS

a. Specific data variables being collected for the study

The primary outcomes are feasibility and acceptability of the intervention and research procedures (Table 1). Study staff will record all feasibility outcomes throughout recruitment, screening, enrollment, and the intervention, data collection, and follow-up phases.

Table 1. PRIMARY OUTCOMES	
Feasibility	
Recruitment	≥70% consent to screening; ≥70% meet screening criteria; ≥70% of eligible enroll; enroll ≥20 participants/month
Eligibility criteria	< 20% ineligible due to each criterion; reasons for ineligibility; reasons for refusal; characteristics of refusers
MBCT and control interventions	Adherence: ≥75% session attendance; retention: ≥75% post-assessments, ≥70% follow-up assessments completed; fidelity: checklist score ≥80%; ≥75% complete home practice at least 3 days/week
Videoconferencing	<20% of connections dropped during session; <20% of sessions missed due to technical problems; number (M<2.0) and type of problems; <20% ask for extra training, type of extra training needed
Blood spots	Adherence: ≥75% submitted at baseline, post-intervention, ≥60% submitted at follow-up; 80% adequate quality
Acceptability	
MBCT and control interventions	Session satisfaction and helpfulness, enjoyment, relevance, utility of each session component (1=not at all, 10=very much; M≥7.5; *post-session survey*); overall program satisfaction (M≥7.5), ≥75% plan to use the skills, ≥75% would recommend the program to others (*post-intervention*

	survey); likes, dislikes, suggestions for improvement (*exit interview*); ≥60% continue meditation practice (*follow-up survey)*
Videoconferencing	Ease and confidence of use (1=not at all, 10=extremely M≥7.5), interference of technical problems (1=none, 10=extreme; M<2.0), audiovisual quality and overall satisfaction (1=poor,10=excellent; M≥7.5; *post-session survey*); pros and cons, suggestions for improvement (*exit interview*)
Blood spots	Ease of data collection and submission (1=not at all, 10=extremely; M≥7.5), level of pain (1=none, 10=extreme; M<2.0; *post-intervention survey*); concerns, suggestions for improvement (*exit interview*)
Note. M = mean. Benchmarks are informed by my pilot data, prior literature and prior clinical trials.	

The exploratory outcomes are within-group changes in health-related variables, measured at baseline, post-intervention, and 3-month follow-up. All self-report measures are validated (Table 2).

Table 2. EXPLORATORY OUTCOMES

Variable	Measurement
Fear of Recurrence	Assessment of Survivor Concerns
Mindfulness	CAMS-R
Resiliency	Current Experiences Scale (CES)
Decentering	Experiences Questionnaire
Depression and Anxiety	Hospital Anxiety and Depression Scale (HADS)
Empathy	Interpersonal Reactivity Index (IRI)
Interoception	MAIA-2 body subscales
Fidelity checklist	MBCT-AS Checklist
Depression	PHQ-9
Health behaviors	Medical Outcomes Study – Specific Adherence Scale (MOS-SAS)
Everyday health	One item from the Short Form-12 (SF-12)
Social connectedness	Self-Other Four Immeasurables (SOFI)
Physical function	PROMIS- Physical Function (PROMIS-PF)
Positive Affect	The Positive and Negative Affect Schedule-Positive Affect (PANAS-PA)
IL6, TNF-α, CRP	Whole dried blood spots

b. Study endpoints

The primary study endpoint is feasibility and acceptability of the intervention at the end of the trial (6 months post-baseline; see Table 1 for more information).

c. Statistical methods

Aim 1. I will calculate frequencies and proportions to assess feasibility outcomes, and means and standard deviations or medians and interquartile ranges to assess acceptability ratings. T-tests or chi-square tests will be used to compare eligible patients who did and did not enroll in terms of demographic and clinical variables, and feasibility and acceptability across enrolled patients based on gender, and medical/psychiatric factors. I will use independent samples t-tests to compare adherent and non-adherent participants from each group on baseline depression and clinical and demographic variables. Exit interviews will be audio recorded, transcribed, and iteratively analyzed using thematic content analysis. Approximately 2-3 members of the study team will review the transcripts to identify common themes and develop a coding framework. We will review our results for agreement and comparison to the raw data, and resolve discrepancies

through discussion with Dr. Park until. All transcripts will be coded according to the coding framework.

Aim 2. Exploratory outcomes. As a pilot feasibility trial, I will explore within-group changes in emotional, physiological, and health behavior variables from before to after the intervention. I will examine frequency distributions for all variables and use non-parametric tests if needed. I plan to use linear mixed effects models with repeated measures and an unstructured covariance matrix to assess changes within the MBCT and control group for the following dependent variables: depression symptoms, inflammation, emotion regulation, pro-sociality, health behaviors, and cardiac health (Table 2). The predictor variables will be time (fixed effect; two levels: baseline, post-intervention) and covariates relevant for each dependent variable (random effects; section 5.1). I will explore follow-up outcomes in separate models where time is a fixed effect (three levels: baseline, post-intervention, follow-up) and covariates are included as random effects, with pair-wise comparisons between follow-up and the other two time-points. I will explore correlations between changes (post-intervention minus baseline) in depression symptoms and inflammation, emotion regulation, pro-sociality, and health behaviors. For dropouts, I will impute missing data using maximum likelihood estimation and, as a sensitivity analysis, the last observation carried forward. For all analyses, trends will be considered based on a two-tailed α=.10.

d. Power analysis

In alignment with the advice of the funding institute (NCCIH) and intended purpose of pilot feasibility trials, we did not conduct a power analysis for this trial. Rather, we selected a sample size (N=40) based on pragmatics, the needs of the trial, and our team's previous pilot studies, that will provide an accurate indication of the feasibility of the research procedures.

VII. RISKS AND DISCOMFORTS

a. Complications of surgical and non-surgical procedures

There are no surgical procedures as part of this study. Given that participants do not need to physically come to the hospital to participate in any study procedures, there is no risk of physical injury to participants.

The process of collecting a dried blood spot sample is relatively painless and non-invasive; however, participants may face minimal discomfort when completing this procedure. Prior to the dried blood spot sample collection, participants will be informed that the procedure may involve mild, temporary pain at the finger prick site and will be provided with suggestions for minimizing any pain that is bothersome (e.g., putting ice on the site). Participants will be sufficiently trained by study staff in how to self-collect their blood samples at home. Participants will be given the option to opt out of any dried blood spot collection points, for any reason. Participants who oppose the provision of dried blood samples will not be

excluded from additional study procedures. In our previous study, it was common for ACS patients to already have experience using the blood spot finger-prick technique for their healthcare and almost all participants expressed comfort and willingness to complete this procedure as part of a research study.

b. Drug side effects and toxicities

There are no drug side effects or toxicities associated with this study.

c. Device complications and malfunctions

There are no risks of device complications.

d. Psychosocial risks

Patients may experience discomfort from completing the survey questionnaires or exit interview and/or participating in the intervention mindfulness trainings or discussions. Participants who do not find the study to provide a benefit to them may find this upsetting as well. All possible measures will be taken to ensure patient comfort and participants will be informed that they could exit the study at any point with no penalty. The PI (licensed clinical psychology) will be available while intervention groups are being conducted to intervene if needed (due to patient discomfort or to answer specific questions about the study). Participants will be informed that they can choose not to complete any surveys or answer any specific survey items or exit interview questions that make them feel uncomfortable, and that they do not need to complete the blood spot procedures. All of these procedures are consistent with sound research design and do not unnecessarily expose subjects to risk.

The main psychosocial safety concern related to patients in this study is worsening depression symptoms and/or suicidal ideation. Subject safety regarding mood and suicidal ideation will be ensured in several ways.

First, eligibility criteria require that patients do not have active suicidal ideation at the time of enrollment, and that they have not been hospitalized for a psychiatric reason in the past year. Thus, it is not likely that participants will report active suicidal ideation during or following the intervention. Moreover, our eligibility criteria require only minimal depression symptoms and thus we do not expect to have a severely depressed sample.

During the eligibility screening procedures, participants will be administered the Patient Health Questionnaire-9 (PH-9) over the phone. If any patient endorses suicidality (i.e., PHQ-9 item 9 score above 0; “Over the past two weeks, how often have you been bothered by thoughts that you were better off dead or of hurting yourself in some way”), the RA will follow our standardized safety assessment protocol that our team has developed and used in prior funded studies of ACS patients with elevated depression symptoms. The protocol involves further assessing safety risks through a series of structured questions, with

specific instructions at each step based on the patients' response. It begins by clarifying the response to PHQ-9 item 9 (i.e., determining passive versus active suicidality). If patients endorse active suicidality, the RA will further assess safety risks (e.g., plan, intent, past suicide attempts) and immediately notify the PI (a licensed clinical psychologist) to conduct further assessment. The PI will conduct detailed suicide assessment of patients with active suicidality and inform the patient's primary treatment providers of the patient's symptoms and assist with the obtainment of further evaluation and care as needed (e.g., through referral to outpatient treatment or to the emergency department [ED]), depending on the urgency of the situation. In our previous work, it has been extremely rare for an ACS patient to report active suicidality that requires intervention.

Upon enrollment, the RA will also conduct proactive safety planning with all participants in the following ways: (1) asking participants to identify 1-2 safety contacts that we would contact in the event that participants become at risk, (2) working with participants to identify the emergency department nearest to their home; (3) and instructing patients to go to this emergency room if they feel unsafe, and inform research staff once they are in a safe place (e.g., hospitalized or back at home). Participants will be asked to report any worsening symptoms to the interventionist during sessions, or in between sessions by contacting the study RA.

For enrolled participants, the PHQ-9 will be administered at baseline, post-intervention, and 3-month follow-up, which will allow us to monitor for worsening depression symptoms. The RA will review changes in participant's PHQ-9 scores over time and contact the participant to discuss any concerns, asking about their symptoms, needs, and concerns about staying in the study, and conducting an initial safety assessment as needed (as described above). The same procedures as described above will be followed if participants endorse suicidality on PHQ-9 item 9 when completing the measure as part of any of the surveys. REDCap will be set up to send automatic alerts to the study staff for any PHQ-9 item 9 responses greater than zero. Participants will be contacted within 24 hours.

The interventionists for each group will observationally monitor participant's symptoms during each weekly intervention session. If the interventionists become concerned based on a participant's presentation during a session (e.g., per their clinical observation or expressed SI by a participant), they will call the participant by phone individually immediately after the session to check in about the participant's symptoms and conduct a safety assessment if needed (following the protocol outlined above). The interventionist will be a licensed mental health provider trained in conducting safety assessments. Interventionists will instruct patients at the start of the first session that if they experience suicidal thoughts or worsening depression symptoms at any point during the study, they should let the interventionist, study staff, and/or their doctors know.

The objective criteria for removal from the study is worsening psychiatric symptoms that become psychiatrically unstable that precludes their participation (e.g., constitute danger to self or others). The RA and interventionist will inform the PI of any concerns about a participant's symptoms and about any contact with participants regarding these concerns. They will let the participants know that if it seems unsafe for them to remain in the study, the PI will contact them. In cases where depression symptoms are worsening but do not constitute necessary removal from the study, the PI will discuss the concerns with the participant, give them the option to exit the study if they would like, and assist them in connecting to a higher level of care if needed (e.g., by providing mental health referrals).

Participants will be provided with an outline of resources for accessing mental health care at the completion of the study.

e. Radiation risks

There are no radiation risks associated with this study.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals

Participants may not benefit from this study. It is hoped that the intervention will result in improved scores on depression symptom measures. The current study may provide training in coping skills for managing depression and improving health behaviors, and promote understanding of depression and cardiac health. It may also provide emotional benefits for participants to share and receive support with their peers and a trained clinician.

b. Potential benefits to society

Developing targeted, efficacious, and accessible interventions to treat depression in ACS patients may have important public health benefits. Depression is common and deadly among acute ACS patients with up to 45% experiencing at least mild depression symptoms. Even mild depression symptoms double the risk of death in ACS patients. Mind-body interventions that are accessible and address the underlying pathophysiology of comorbid depression and cardiovascular disease are needed, and the MBCT intervention being tested in the current stay has the potential to address this need. This study will establish the feasibility and acceptability of the intervention and inform targets for refinement in a future R01 efficacy trial. Thus, participation in this study may result in the development of an innovative, efficacious, and accessible depression treatment that can have substantial benefit to future ACS patients.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data

Source materials will include information collected from survey questionnaires at baseline, post-intervention, and 3-month follow-up; exit interviews; weekly practice logs; post-session surveys; and blood spot collection procedures. All self-

report questionnaires will be entered electronically via REDCap. Individual exit interviews will be conducted by phone or videoconferencing. Upon their receipt, all dried blood spot samples will be stored securely in an MGH affiliated lab, on the MGH campus. Samples will later be shipped, in accordance with MGB and CDC guidelines, to our collaborators Dr. David Victorson and Dr. Thomas McDade at Northwestern University for storage and/or processing. All samples will be labeled with the patient ID, date of collection, group assignment, and time point (baseline, post-intervention, 3-month follow-up). We will follow all CDC shipping guidelines (e.g., placing a freeze pack inside of an insulated shipping container, placing sealed plastic bags containing the samples into a box). We will seal the box tightly with tape and ship specimens via courier to Dr. Victorson's Consciousness in Health Lab at the Northwestern University Feinberg School of Medicine.

Dr. Victorson will securely store the samples in his locked lab at Northwestern before bringing them for processing to his collaborator Dr. Thomas Dade at the Laboratory for Human Biology Research at Northwestern University. The blood samples will not contain identifiers that could be used by the outside collaborators to link the data to individual subjects; they will be labeled with participants' study ID numbers and not any personally-identifying information, and only Partner's study staff will have access to the data file linking participant's personal information to their study ID number. Study staff have completed CDC and HealthStream trainings on dried blood spot storage and shipping and have acquired the proper documentation to ship samples to a non-MGB lab.

All information collected will be for the purposes of research and will only be accessible to study staff and stored securely on the Partners' network. Survey and practice log data will be reviewed for completeness though participants will be allowed to skip any questions they are not comfortable answering.

b. Safety monitoring

The principal investigator is responsible for data and safety monitoring. If study staff becomes aware of any adverse events, the event will be reported immediately to the PI.

c. Outcomes monitoring

Outcomes will be monitored via scores on self-report questionnaires at baseline, post-intervention, and 3-month follow-up. Participants will also be monitored during weekly MBCT and health enhancement control sessions. Study staff (licensed clinical psychologist, LCSW) will be available to respond to any worsening in outcomes. REDCap will be automated to inform the RA and PI of any endorsements of suicidality, so that the study team can follow up with these patients immediately.

d. Adverse event reporting guidelines

All PHRC guidelines will be followed with respect to reporting unanticipated problems, including adverse events. Specifically, when a serious or non-serious adverse event occurs, the PI will review the event to determine if it was possibly or definitely related to participation in the research. For all unanticipated problems and adverse events deemed related or possibly related to the research, a member of the research team will complete and submit an Other Event report through Insight/eIRB as soon as possible and within 5 working days / 7 calendar days (as defined in the March 2014 Reporting Unanticipated Problems Including Adverse Events report). At Continuing Review, a summary of all unanticipated problems will be provided as per PHRC protocol. Finally, if there are unanticipated problems, especially if serious or recurrent, the PI will amend the protocol if it is deemed necessary to protect the safety and welfare of the participants.

X. References