Mindfulness-Based Stress Reduction for Adults with Low-Risk Chest Pain Associated with Anxiety: A Pilot Trial

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1. Background

Patients who present with chest pain accounted for approximately 7 million visits to US Emergency Departments in 2011 [1]. Most resources, research and clinical efforts focus on detection and treatment of acute coronary syndrome (ACS); however, about *80% of all patients presenting to Emergency Departments with complaints of chest pain do not have cardiac disease or any other cardiopulmonary emergency by conventional testing* [2-8]. Thus, these patients display the symptomatic syndrome of non-cardiac chest pain, also referred to as low risk chest pain (LRCP), specifically, angina-like pain in the absence of coronary stenosis [2, 8-11]. Studies suggest that 50-80% of these patients go on to *develop low-risk chronic chest pain* and continue to seek medical attention despite negative cardiac evaluations and reassurance [4, 12]. Further, previous findings indicate that up to 55% of patients diagnosed with LRCP may suffer from anxiety or panic disorders, and these psychiatric disorders remain undiagnosed in almost 90% of cases [5-9, 13-21]. Additionally, while epidemiologic data estimates the 12 month prevalence of anxiety disorders in the general population to be approximately 18% [22, 23], these psychiatric disorders are absent from the top 20 discharge diagnoses of patients from US emergency departments based on ICD-9 codes [1].Thus, patients with low-risk chest pain associated with anxiety (LRCP-A) do not get the true care and management they require and continue to access the healthcare system inappropriately. The cost for LRCP evaluations is estimated to be approximately $8 billion per year, usually with no definitive cause contributing to recurrent ED visits [24, 25]. *Conventional emergency care practice ignores this opportunity to improve patient health and health service delivery*. Usual ED care to exclude ACS and other cardiopulmonary emergencies can require 6-48 hours, multiple tests, radiation exposure, and high cost [26]. Moreover, emergency clinicians perceive that their primary duty in the ED is to treat life-threatening issues. Our exploratory data demonstrate that physicians believe they currently lack the necessary evidence-based resources to comfortably detect and initiate treatment for patients with contributing psychological and psychiatric factors [27]. This leaves ED clinicians unable or unwilling to explore the psychological causes of LRCP. Our work will provide the first step toward introducing evidence-based solutions for the identification and management of patients with LRCP-A.

One of these solutions could involve mindfulness-based stress reduction (MBSR) as a means to help patients manage their anxiety. MBSR is a structured meditation training program originally developed by Kabat-Zinn to assist adults in managing chronic pain [28]. MBSR has also been used widely to manage chronic disease processes and their psychological comorbidities [29-35]. MBSR has been shown to have a positive effect on individuals with either comorbid anxiety symptoms or anxiety disorders [31, 36-42]. MBSR usually consists of 8-10 weekly group sessions aimed at developing mindfulness skills which focus on non-judgmental moment to moment awareness through meditation, yoga, and psychoeducation [31]. Through guided training in mindfulness meditation practices, individuals trained in MBSR learn to focus their attention on present-moment experiences with an attitude of open curiosity and acceptance, facilitating adaptive coping with stress and stress-induced physical sensation.

The theoretical basis for the positive effect of mindfulness is that it supports the cultivation of emotional regulation skills through decreases in the habitual tendency to react to and ruminate about transitory thoughts and physical sensations[36, 43-46]. This emotional regulation has been shown to occur through strengthening prefrontal cognitive control mechanisms and downregulation of regions responsible for affective processing, such as the amygdala [44, 47]. Panic, anxiety and worry are often underpinned by overwhelming thoughts about what will happen in the future along with catastrophic misinterpretations of bodily sensations. Thus, it has been theorized that “present-moment mindful awareness may provide a useful alternative way of responding for individuals with generalized anxiety disorders” [48]. This intervention may provide patients with LRCP-A with the tools necessary to respond adaptively to present moment thoughts, feelings, and bodily sensations that may drive their recurrent episodes of anxiety associated chest pain [49].

2. Rationale and Specific Aims

Hypothesis: ED patients with LRCP-A can be accurately identified and successfully referred for MBSR leading to improved patient-centered outcomes. These hypotheses will be tested by the following two *Specific Aims*:

Specific Aim 1: To determine the feasibility of employing rapid cardiac risk stratification and psychological screening to identify patients with LRCP-A in the ED for subsequent referral to MBSR. Currently there are no tools regularly used in the ED to screen for LRCP-A, however, our *working hypothesis* is that evidence-based tools can be used to identify patients at risk for LRCP-A. To accomplish this, we will execute

a two-step prospective screening approach: 1. Determine score on the validated and widely used HEART scale [50, 51]. 2. Those with a HEART score <4 will complete the General Anxiety Disorder 7-item (GAD-7) questionnaire. Scores ≥10 are indicative of the criterion standard for moderate to severe symptoms of anxiety [52]. In this pilot study, feasibility will be assessed in a number of ways including the determination of the rate of eligible subjects per month, proportion of eligible subject who enroll, and proportion who complete the MBSR intervention. *Expected outcome:* This aim is designed to provide data regarding the feasibility of the risk stratification, psychological screening, and MBSR referral approach.

Specific Aim 2: To determine the effect of an MBSR training program for patients with LRCP-A on mental health (longitudinal GAD-7 scores, quality of life (PROMIS Global Short Form), and ED resource utilization (return ED visits). *Our working hypothesis* is that early referral to MBSR will help patients better regulate their thoughts, feelings, and bodily sensations related to their anxiety symptoms and have a significant positive effect on patient-centered outcomes such as mental health, quality of life as well as decreased ED resource utilization. To this end we will assign LRCP-A patients identified in SA1 to usual care referrals versus MBSR. We will then follow these patients for outcomes including change in GAD-7 scores, PROMIS Global Short Form, ED utilization among other outcomes at 6 weeks, 3 months, 6 months, and 1 year. *Impact:* This aim will establish a viable and novel treatment pathway for ED patients identified to be at risk for LRCP-A to ensure the possibility of early directed intervention.

3. Inclusion/Exclusion Criteria

Inclusion:

- Age: *18 through 70*
- Chief complaint of chest pain
- HEART Score of 0-3 indicating Major Adverse Cardiac Events (MACE) risk equivalent to ≤2%
- GAD-7 score ≥ 10

Exclusion:

- Age <18 or ≥ 71
- Chief complaint of anxiety, panic, or similar
- Prior personal ACS history (known at time of provider interview)
- Previous enrollment in the study
- Traumatic injury to the chest
- Suicidal ideation or active psychosis or behavioral issues requiring psychiatric monitoring
- Hemodynamic instability
- Non-English speaking
- Potential issues affecting follow up
    - Prisoners, homeless patients, out-of-town residences

4. Enrollment/Group Assignment

We will screen patients presenting to the Methodist ED with the chief complaint of chest pain. Sources for this information include the ED tracking systems and electronic medical records systems. Patients will be evaluated with the HEART score by their treating physician to determine if the patient initially qualifies to participate in the study. The treating physician will provide the information necessary to calculate the HEART score. Qualifying subjects will then be approached for final eligibility assessment using the GAD-7 and consented if interested and eligible.

Enrolled subjects will be assigned to either arm depending upon enrollment period. In the 8 weeks prior to the MBSR course commencement all subjects enrolled will be assigned to Arm 2: MBSR. This period will be immediately followed by 8 weeks of enrollment in Arm 1: Standard Referral. To decrease subject bias with regard to the interventional arm, potential enrollees will remain blinded to the enrollment period until informed consent is complete. This method of assignment has been chosen to help maximize intervention enrollment given the limited recruitment period.

5. Study Procedures (see figure 1 for an overview of protocol)

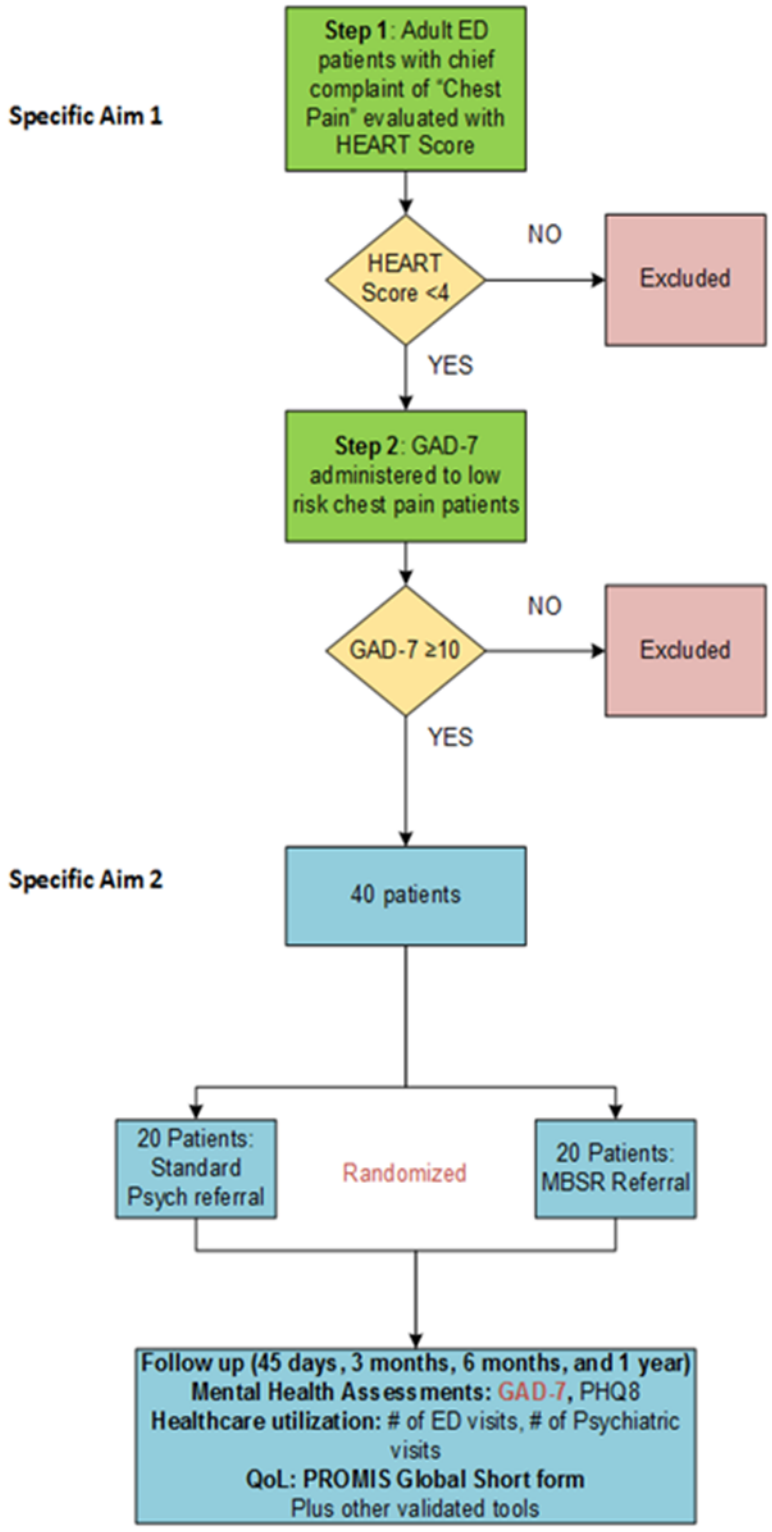
Figure 1 illustrates an overview of the flow of screening and enrollment for both specific aims. The patients who screen eligible in Aim 1 are the population of interest for assignment in Aim 2. The goal is to assign 40 subjects for the intervention arms. Each enrolled subject will have follow up evaluations at 45 days, 3 months, 6 months, and 1 year. Two ED physicians will independently review medical records of each enrolled patient for the described outcome variables and adjudicate any discordances by consensus.

Specific Aim 1: To determine the feasibility of employing rapid cardiac risk stratification and psychological screening to identify patients with LRCP-A in the ED for subsequent referral to MBSR.

Under a waiver of informed consent for recruitment, we will initially screen patients between the ages of 18 and 70 who present to Methodist Emergency Department (ED) in Indianapolis, IN. We will assess their risk for major adverse cardiac events (MACE) using the HEART score [50, 51]. This score is a validated tool, which is used to risk stratify patients who present to the ED with chest pain and to predict the 6-week risk of MACE. The HEART score defines MACE as all-cause mortality, acute myocardial infarction, or coronary revascularization [53]. This tool assigns a numeric score from 0-9. A score of 0-3 corresponds to a low risk, with less than 2% risk of MACE. Scores of 4-6 indicate moderate risk, and scores of 7-9 are considered high risk. Patients who score between 0 and 3 on the HEART score, indicating a low risk for MACE, will be approached for final eligibility determination using the self-report GAD-7 questionnaire.

The GAD-7 [54] is a rapid screening tool for the presence of a clinically significant anxiety disorder such as General Anxiety Disorder (GAD), Panic Disorder (PD), Social Phobia (SP) & Post Traumatic Stress Disorder (PTSD) in outpatient settings. It has been prospectively validated and is used to objectively determine symptom

Figure 1: Protocol Overview



severity and monitor symptom changes and effect of treatment over time. It is comprised of 7 items with an unscored item which assesses patient-rated global impression their symptom related impairment. The scores range from 0-21 with cutpoints at 5, 10, and 15 for mild, moderate, and severe anxiety, respectively. A cutoff of 10 has a sensitivity for generalized anxiety disorder of 89% and specificity of 82% with test-retest reliability of ICC=0.83 [52, 55]. Patients who score ≥10 on the GAD-7, indicating at least moderate levels of anxiety, will be eligible for enrollment if their ED provider agrees with the high likelihood of LRCP-A. We plan to delay informed consent until after the GAD-7 determination for practical purposes as having knowledge regarding the study objective may affect the patient's responses the GAD-7. Patients will have opportunity to consent to retain the collected information as well as continue on with the study. For ineligible subjects, we will only retain counts and total scores for feasibility calculations but no identifiable information will be kept. For eligible patients, trained research personnel (investigator, research assistant, or social worker) will discuss the results of the screening tests with the patient and introduce the study and a research assistant or coordinator will obtain informed consent for assignment from interested subjects. Those who enroll will answer questionnaires assessing the domains presented and described further in table 2 below.

Outcome assessments:

1. Protocol feasibility will be assessed via patient eligibility, recruitment, and retention.
    a. Rate of eligible patients: # of eligible patients per month based on heart score, and the % of those patients who have an eligible GAD-7 score. We believe that 30% of subjects screened will be eligible for enrollment based on prior work.
    b. Proportion of eligible patients who enroll. Based on prior work with this population in an observational study, our target is 40%.
    c. Proportion of enrolled patients with an intervention session or follow up visit. We aim to have 75% of those assigned to MBSR complete at least 1 session.
    d. Proportion of enrolled patients who complete the study and follow up evaluations. We aim to show that 70% of those assigned to MBSR will complete at least 6/8 intervention sessions. Additionally, assuming a 10% loss to follow up at each follow up time point we expect to have 65% who have completed all follow up evaluations.
    e. Time to first follow up PCP or mental health professional visit.

2. The presence of MACE at 45 days as defined by the following diagnostic criteria:
    a. Any death of an enrolled patient within 45 days of index ED visit.
    b. Acute myocardial infarction and coronary revascularization as defined in the Third Universal Definition of Myocardial Infarction.[56]
    c. Electronic medical record (EMR) review to assess intervening significant cardiopulmonary related diagnoses at 45 days.

Specific Aim 2: To determine the effect of an MBSR training program for patients with LRCP-A on mental health (longitudinal GAD-7 scores, quality of life (PROMIS Global Short Form), and ED resource utilization (return ED visits).

Forty subjects who screen positive for LRCP-A using the process outlined above will be assigned to one of two treatment arms. Enrolled subjects will be referred for standard primary care and/or psychiatric referral for therapy using IU Health's existing consult and referral infrastructure (Arm 1) or for therapy sessions using MBSR (Arm 2) [28, 31]. We plan to recruit eligible subjects for assignment in the 40 days prior to the start of each 8-week MBSR class series.

1. **Arm 1: Standard psychiatric referral:** Subjects will be referred for primary care provider (PCP) follow up and/or to psychiatry for further management and treatment of elevated anxiety levels according to standard of care. The treating ED provider will have discretion as to which referral option they believe to be more appropriate for each patient. This will occur using the hospital system's current infrastructure and act as a "time from referral to treatment" control. Thus, we will have a baseline for the average time it would take for an individual referred for evaluation or treatment to be seen. Subjects will receive a standard set of discharge instructions which will discuss anxiety, chest pain, and instructions for follow up with their PCP. For those patients without a PCP, we will provide a list of PCPs with whom they could establish care. Patients will also be given a resource list of mental health professionals with whom they

could also schedule follow up with if directed by the ED provider. This list will be a custom list provided by our social work colleagues based upon individual patient factors (proximity to residence, insurance status, etc.) which is currently standard practice. We plan to also send a letter or EMR communication to the patient's PCP if they have one alerting them to their participation in the study, their study assignment, and encouraging further evaluation and management of their anxiety symptoms. For those without a PCP at time of enrollment we will query the patient at each follow up time-point for the establishment of primary care and send this letter if they have been able to do so at that time.

2. **Arm 2: MBSR intervention:** In addition to the standard referrals and discharge instructions discussed above, subjects assigned to MBSR will be offered a referral to a local MBSR course. The standard MBSR course meets one day per week for 8 weeks, with sessions being 2.5 hours in duration. A full day retreat (7 hours in length) is offered on a Saturday between sessions 6 and 7. The primary techniques are the "body scan", a noncritical assessment of bodily sensations when directing attention in a deliberate manner from the feet through the head and focused meditation with a special attention to breathing [57]. The full training program is presented in the intervention instruction manual and Table 1 outlines the contents of each weekly session. Our study interventionist will provide several options for the MBSR course (e.g., different days of the week and times of day) from which to choose to maximize convenience. To maximize MBSR availability for this pilot, these blocks will include groups open to non-study participants as well as closed dedicated study groups.

Table 1. Description of Mindfulness-Based Stress Reduction Sessions

Session #	Session Themes	Meditation Exercises	Didactic Teaching	Home Practice
Orientation	Describe mindfulness in words and embodied engagement. Explanation of participant commitment to actively engage in class participation and daily mindfulness practice.	▪ Provide participants with an experience of mindfulness in an atmosphere of trust and non-judgmental awareness.	▪ Familiarizing potential participants with what MBSR is and is not. ▪ Explain class logistics and content. ▪ Examples of clinical evidence of MBSR program. ▪ Describe possible physical, emotional, social, and time risks and benefits.	▪ Meet with each participant individually for a brief screening interview. ▪ Describe formal and informal home practice. ▪ Explain what to wear and bring to class.
1	Describe and experience theoretical underpinnings of mindfulness. Explain development of regulatory skills in formal practice and meeting ourselves where we are in honesty and kindness.	▪ Raisin exercise ▪ Body scan ▪ Brief mindful movement (MM).	▪ Participants introduce themselves and begin building trust within the group as a learning community. ▪ Establish contract of confidentiality.	▪ Practice body scan daily. ▪ Eat one meal mindfully (handout provided). ▪ Mindfulness of one daily activity.
2	Experiential mindfulness skill development. Wholeness no matter what is here.	▪ Body scan ▪ MM ▪ Awareness of breath (AOB) sitting meditation	▪ Perception and creative responding: how we see things determines how we respond. ▪ Explore universality of the wandering mind and how to work with this and other challenges in practice.	▪ Continue body scan practice. ▪ Bring MM into daily movement. ▪ Sit quietly 10 min daily with AOB. ▪ Pleasant events calendar. ▪ Mindfulness of another daily activity.
3	The pleasure and power of embodied presence: Investigating knowing how things are in the body and mind in the present moment through	Integrating and expanding multiple practices: ▪ MM ▪ Body scan ▪ Sitting meditation ▪ Possible walking meditation	▪ Reflections and challenges of direct experience in formal and informal mindfulness practice. ▪ Pleasant events reflection: appreciating	▪ Alternate body scan and MM daily ▪ AOB 10-20 minutes ▪ Unpleasant events calendar ▪ Mindfulness of daily activity

	formal and informal practice.		what we have in the present moment.	
4	Exploration of mindfulness as a means of recognizing and reducing negative effects of automatic, habitual stress reactivity Supporting healthy responsiveness	▪ MM ▪ Body scan ▪ Sitting meditation All practices with emphasis on concentration, embodiment, and capacity to redirect attention.	▪ Stress reactivity (fight-or-flight response) ▪ Exploration of reactivity in health and illness ▪ Development of more effective ways of responding pro-actively to stressful situations and experiences	▪ Alternate body scan and MM daily ▪ Unguided sitting meditation 15-20 min daily ▪ Unpleasant events calendar ▪ Be aware of automatic stress reactions during the week without trying to change them
5	Exploring conditioned patterns as previously adaptive but no longer functionally adaptive Awareness of mind/body patterns as a doorway to adaptive responses to everyday challenges and stressors	▪ Open awareness sitting meditation ▪ MM ▪ Body scan ▪ On-the-spot brief practice for use in times of stress if not previously introduced	▪ Theories and studies of mindfulness developing stress hardiness and resilience. ▪ Expanding ways of working with uncomfortable physical sensations and emotions ▪ Emotion- and problem-focused coping reflection	▪ Alternate new guided sitting meditation, MM, or body scan daily ▪ Problem- and emotion-focused coping handout ▪ Reading on mindful communication ▪ Challenging communication calendar
6	Continuing to enhance stress hardiness through mindfulness Identifying and expressing emotions accurately and mindfully Exploration of stress in the domain of communication: cultivating mindfulness in listening and speaking	▪ Open awareness sitting meditation ▪ MM ▪ Possible walking meditation	▪ Communication styles explored didactically and experientially ▪ Mindful listening and speaking skills ▪ Embodiment in exploring flexible ways of communicating in challenging interpersonal interactions	▪ Alternate sitting meditation, MM, or body scan daily ▪ Emphasis on observation and application of mindfulness in daily activities
Retreat	Establishing mindfulness in multiple situations; cultivating mindful attention from moment to moment and being open to any experience, whether evaluated as pleasant, unpleasant or neutral Seamless awareness moment to moment.	▪ MM ▪ Sitting meditation ▪ Body scan ▪ Lake meditation ▪ Walking meditation ▪ Outdoor visual meditation ▪ Lovingkindness mediation	▪ Talk drawing on a core theme of class that gives encouragement	▪ Alternate MM, sitting meditation, body scan, and lovingkindness mediation; participants are also encouraged to create their own flexible blend of practices for 45 minutes ▪ Continue application of mindfulness in daily activities including communication
7	Taking care of yourself: healthy living choices arising from practice Mindfulness as a means to explore the familiar and the unfamiliar	▪ Self-guided MM ▪ Sitting meditation ▪ Lovingkindness practice	▪ Mind/body input; reflecting on what is nurturing/depleting ▪ Connect what was experienced in the all-day retreat and afterwards to automatic habitual stress reactions and	▪ Daily sitting meditation, MM, or body scan ▪ Practice informally by pausing throughout the day and resting in awareness ▪ Develop plan for continuing practice

			mindfulness-mediated stress responses in meeting whatever was encountered	
8	The rest of your life: Making the practice your own	▪ Body scan ▪ MM ▪ Sitting meditation	▪ Review of the course with an emphasis on daily strategies for maintaining and deepening mindfulness skills ▪ Sharing of participant perspectives on the program; welcoming all comments	▪ Mindfulness resources handout ▪ Continuing the practice & making it your own ▪ Bringing seamless attention to life

Outcome assessments: The schedule of assessments is shown in Table 2. These assessments will take place in the method most convenient for the patient (telephone, mail, or online REDCap survey completion). These are all methods the PI and his research team are currently using. **The primary outcome of interest will be the mean longitudinal change in GAD-7 scores between intervention groups at each time point.**

Table 2. Assessed Domains

Domain	Measure	# of Items	Time Period Investigated				
			ED	45 day	3 mo	6mo	12mo
MACE[1] Risk	HEART Score	5	x				
ACS Risk	PreTest Consult ACS	8	x				
Demographics	Age, Race, Gender, Education etc.	10	x				
Medication Use	Standard Items	2	x	x	x	x	x
Medical Comorbidity	9-Condition Checklist	9	x				
Chest Pain Symptoms	Custom Items and Numeric Rating Scale	5	x				
Somatization	Patient Health Questionnaire (PHQ-15)	15	x	x	x	x	x
Anxiety Severity	Generalized Anxiety Disorder Scale (GAD-7)	7	x	x	x	x	x
Panic	PHQ Panic Scale	5	x	x	x	x	x
Social Anxiety	Mini-SPIN	3	x	x	x	x	x
PTSD	4-Item screen	4	x	x	x	x	x
Depression	Patient Health Questionnaire (PHQ-8)	8	x	x	x	x	x
Cardiac Anxiety	Cardiac Anxiety Questionnaire	18	x	x	x	x	x
Resilience	Brief Resilience Scale	6	x				
Pain Catastrophizing	Pain Catastrophizing Scale	13	x				
Healthcare Utilization (12 mo Pre-ED)	Custom Items	6	x				
Healthcare Utilization (Post-ED assessment)	Custom Items	6		x	x	x	x
Healthcare Related Quality of Life	PROMIS Global Short Form	10	x	x	x	x	x
Life Trauma	Traumatic Life Events Questionnaire	18	x				
MBSR Mechanism of Action	Cognitive and Affective Mindfulness Scale-Revised (CAMS-R)	10	x	x	x	x	x
MBSR Evaluation	Toronto Mindfulness Scale (TMS)	13	x	x	x	x	x

[1]Major Adverse Cardiac Event

Subject Compensation: Subjects who enroll after informed consent will receive compensation for their time spent answering validated surveys and follow up evaluations. Enrolled subjects in both arms would be eligible for up to $160 in direct which will be structured as follows: $40 for the ED interview and another $30 for completing each of the follow-up phone evaluations (45 day, 3 months, 6 months, and 1 year). These payments will be in the form of generic gift cards which will be disbursed at the completion of each follow up evaluation. Because the MBSR intervention involves travel to a non-hospital site that is not always easily accessible by public transport, these subjects will be eligible for additional compensation to defray travel costs ($10/session attended) to be paid at end of MBSR course. The study will also provide indirect compensation to those assigned

to ARM 2 (MBSR) by covering the cost of their therapy sessions ($350), which would be paid to the interventionist if the subject attends.

Fidelity Monitoring: We will utilize strategies across four domains to ensure treatment integrity in the MBSR arm and minimize protocol deviations.[58] Co-Investigator Dr. Shelley Johns has expertise in MBSR research and will oversee this process. Additionally, at each of the 4-specified time-points for follow up, we will assess via EMR review if mindfulness interventions have been used in the management of subjects in the psychiatric referral arm.

1. **Study design**— The MBSR intervention will be delivered consistently with the standardized MBSR manual developed at the Center for Mindfulness in Medicine, Health Care, and Society at the University of Massachusetts, where MBSR was developed [59].
2. **Treatment delivery**— Interventionists will keep field notes to document duration, frequency, and uptake of study conditions. EMR review will be performed for those assigned to standard psychiatric referral to obtain information regarding treatment.
3. **Treatment receipt**—use of engaging therapeutic activities to increase participants' practice of skills; interventionist provision of frequent summaries of session content and query of participants' understanding and active use of session material; collection and review of participant self-monitoring data.
4. **Treatment enactment**—Mechanisms of action specific to mindfulness as assessed with the Toronto Mindfulness Scale (TMS)[60] and the Cognitive and Affective Mindfulness Scale **(**CAMS-R)[61] will be measured to assess intervention receipt and enactment.

6. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

All adverse and severe adverse events will be reported in compliance with IU regulations. Some anticipated adverse events include discomfort with the subject material and psychological distress when thinking about stressful events. Participants will be able to decline to answer any questions or withdraw at their discretion, which will help to alleviate this risk. Subjects found to have severe depression at any time point as assessed by a PHQ-8 score > 19 will be referred for depression specific treatment. Subjects who disclose suicidal ideation or have active psychotic symptoms during the initial ED interview will not be eligible for continued participation and will be directed to seek appropriate care in the Emergency Department. If they disclose suicidal ideation or exhibit active psychotic symptoms at follow up the PI will be immediately contacted to evaluate for the need for intervention (referral to the ED, notification of the PCP etc.). There is also a risk for loss of confidentiality. Participants' paper and electronic records will be appropriately protected to help minimize this risk.

7. Study Withdrawal/Discontinuation

Participants will be able to withdraw themselves from the study at any point in time without issue. The PI may withdraw the patient from this study if the participant is unresponsive and/or unable to participate in a timely manner.

8. Statistical Considerations

The goals are to collect preliminary data regarding the feasibility and effectiveness of the MBSR referral and approach compared with standard of care referral. Eligibility, recruitment, and retention information will be tabulated. Frequencies and percentages will be summarized by group for categorical variables, and continuous and count variables will be summarized by group using the mean, standard deviation, and range. The primary outcome of interest will be a comparison of the mean change in GAD-7 scores at 3 months using the t-test. Secondary analysis will look at the comparison of mean change in GAD-7 longitudinally using repeated measures ANOVA. The repeated measures ANOVA will compare scores between groups and compare scores over time within groups. Similar analyses will be used for the other efficacy outcomes. The proportion of subjects with a visit, time to first visit, and number of visits will be compared using chi-square, log-rank, and Wilcoxon rank sum tests, respectively. A 5% significance level will be used for all tests.

Because there is minimal published data to guide power calculations in this population for our outcome of interest we have chosen a sample size of 12 for each interventional arm in this pilot study on the basis of feasibility as described by Julious [62]. This sample size of 12 will be increased to 20 per arm to account for an

estimated 40% drop out rate prior to completion of the MBSR intervention. Thus, the total number of subjects we expect to enroll to the intervention is 40. All subject data will be analyzed on an intention to treat basis.

9. Privacy/Confidentiality Issues

All information will be entered and REDCap Software Version 7.0.10 - © 2017 developed by Vanderbilt University (licensed to Indiana University) will be used for all data entry and survey tools. The patient's health information used in these analyses will be protected by a number of mechanisms. Collaborative Institutional Training Initiative (CITI) training in the protection of patient confidentiality will be required of all research assistants and coordinators involved in the study. All interviews will occur in a patient care area with all efforts to provide privacy. Participants' paper records will be stored under double locks. All electronic records will be behind password protection and firewalls, including secured department shared drives and/or REDCap. Research personnel will be provided with usernames and passwords in order to access electronic subject records or to use the EDC system. Data analysis will be performed on de-identified information.

10. Follow-up and Record Retention

Chart review and/or patient follow-up will be performed at the 4-specified time-points: 45 days, 3 months, 6 months, and 12 months. After the final scheduled follow up, the patient's record will then be de-identified. Study records will be retained according to the longest most applicable timeline according to federal, state and institutional regulations from the close of study with the IRB. After this timeline has been reached, study records will be destroyed according to the policies of the archive repository contracted to house these records.

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