Asthma Symptom Management through Mindfulness Training: A Multi-Site Randomized Controlled Trial of the Effect of Mindfulness Based Stress Reduction (MBSR) on Asthma Control

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Version 12

Tool Revision History

Version Number: 1
Version Date: 11-26-14
Summary of Revisions Made: Original

Version Number: 2
Version Date: 2-26-15
Summary of Revisions Made: Minor revisions to text and assessment table to be consistent with final study questionnaires (e.g., noted quality of life measure was 32 and not 30 items; added # of years taking asthma medication; changed items re: days of work/school missed and CAM use from 14 days to 6 months; added to assessment table asthma triggers and months when asthma is worse)

Version Number: 3
Version Date: 7-13-15
Summary of Revisions Made: The 4-week window between orientation and intervention start was extended to eight weeks to allow a time frame that provided sufficient options for participants to schedule their baseline respiratory assessment visit within their availability to attend. Figure 6 and the text of Sections 4.3, 5.2, and 6.2.2 were amended to reflect that change.

A typo in Section 4.2 Exclusion Criteria was corrected from 'Diagnosis of asthma of intermittent severity' to 'Diagnosis of intermittent asthma'.

Version Number: 4
Version Date: 11-18-15
Summary of Revisions Made: Frequency of DSMB meetings was changed from quarterly to annually to reflect the low-risk nature of the interventions. Sections 7.6 and 10.3.2 were edited to reflect this change.

Randomization blocks were changed from four to six, to blocks of two as a precaution against most patients coming from the moderate severity group given the distribution of disease severity in the population. Sections Precis, 3.0, 4.3, 6.2.2, 9.2 and 11.2 were edited to reflect that change.

Version Number: 5
Version Date: 5-23-16
Summary of Revisions Made: Eligibility criteria (Sections 4.1 and 4.2) were edited to clarify (Smoking Hx, Cancer, Cardiovascular disease Hx, Psychiatric Hx, Pregnancy).

Enrollment and Recruitment Procedures (Section 4.3) modified to enhance recruitment from pulmonary clinics and the clinical system.

Clarification of number of classes attended and homework completed (Section 5.4) to constitute a protocol deviation.

Minor changes to screening and consent procedures (Section 6.2.1 and 6.2.2).

Asthma severity classification procedures clarified (Section 6.2.2).

Monthly data audits were specified (Section10.2).

Modification to note opt scannable forms are not used (Section 10.3).

Version Number: 6
Version Date: 7-11-16
Summary of Revisions Made: Additional cancer screening questions (Section 4.2)

Clarification of Miriam site recruitment procedure (Section 4.3).

Modification of AE procedure following ≥15% decrease in spirometry from baseline: After consultation with Dr. Madison, it was decided that we would communicate the PFT change to the patient's pulmonologist/physician and allow the physician to decide if/how to follow up with the patient (Section 7.4).

Clarification of severity classification and procedure (Section 6.2.2).

Edited to standardize protocol terminology with CRF and RedCap ('Screening Form', Sections 4.3, 6.2.1 and 11.2; 'home assignments' to homework, Sections 5.1, 5.4; 'Breath perception discrimination task' to Breath perception discrimination test', Sections 1.2, 9.5.2; Deviations documented to Deviations logged, Section 10.3.4; End of study to Study completion, Section 9.6).

Version Number 7
Version Date: 7-29-16
Clarification and implementation of protocol revisions through site visits (Section 10.3.5).
Modification of evidence of bronchial hyper-responsiveness eligibility criterion (Section 4.1)

Version Number 8
Version Date: 8-29-16
Revision of data quality control procedures (Section 10.3.3).

Version Number 9
Version Date: 12-05-16
Revision of study team roster changing Dr. Ghada Bourjeily to Principal Investigator for Miriam.

Version Number 10
Version Date: 1-20-17
Because yoga practiced for fitness is unlikely to confound intervention effects, the exclusion criterion of 'regular practice of yoga' was modified to 'Has taken the MBSR program in the past, and/or is currently practicing meditation or yoga that includes a meditative component at least weekly for the past 2-3 months' Section 4.2).

Question asking if patient has ever taken a Healthy Living Course added to Phone Screen to increase equipoise.

Question added to 6-Month Follow Up assessment asking those who attended four or fewer intervention classes their reasons for non-attendance (Section 6.2).

Version Number 11
Version Date 4-23-18
Additional strategies to strengthen participant attendance at intervention classes, and additional sources and strategies for recruitment (Section 4.3).

Clarification the intent-to-treat principle is used in the primary analysis and that the data will also be analyzed per protocol (versus actual interventions received) (Section 9.3).

Version Number 12
Version Date: 9-2-20
Where travel restrictions or personal distance requirements due to the COVID-19 pandemic restrict on-site visits, staff at each site will request approval from their IRB to allow remote access to NCCIH monitors to review of records, consents and study files on-line (Section 10.3.5).

STUDY TEAM ROSTER

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PRÉCIS

Study Title Asthma Symptom Management through Mindfulness Training: A Multi-Site Randomized Controlled Trial of the Effect of Mindfulness Based Stress Reduction (MBSR) on Asthma Control

Primary Objective is to **e**valuate whether asthma control improves more in MBSR participants than in participants in a healthy living control program (HLC) at 18-month follow-up.

Secondary Objectives are to evaluate whether, compared to HLC, MBSR results in improved:

1. Asthma-related quality of life (QoL) from baseline to 18-month follow-up.
2. Respiratory interoceptive accuracy and whether this has a mediating effect on asthma control, QoL, and medication use.
3. Lung function (change from baseline in 2-week average morning peak expiratory flow (PEF), and spirometry (Forced Expiratory Volume in 1 second (FEV_1)).
4. Cost-effectiveness in asthma control and management.

Design and Outcomes: This is a 5-year randomized controlled trial to evaluate the effect of MBSR on asthma symptom management as reflected in level of asthma control at 18-month follow-up. Two hundred and fifty four patients 18 years and older with documented mild, moderate or severe asthma[1, 2] will be recruited from the patient population of UMass Memorial Health Care (UMMHC) and the Miriam Hospital. Respiratory and psychosocial assessments will be at baseline, and 6- 12-, and 18-months post-baseline.

Interventions and Duration: MBSR will be compared to the Healthy Living program that controls for time, attention and participant demands. Each participant will be on-study for a period of 18 months.

Sample Size and Population: The study sample of two hundred and fifty-four patients will be drawn from a population of individuals eighteen years and older with a documented diagnosis of mild, moderate or severe asthma from a physician. Participants will be randomized to either MBSR or the HLC control. Randomization will be stratified by site and asthma severity with each stratum in randomly allocated block sizes of two using the ralloc program in Stata. The randomization will be carried out within each cohort to ensure the effects of seasonality and temporal trends be adequately controlled by design.

1. STUDY OBJECTIVES

1.1 Primary Objective: The primary objective is to evaluate the effect of MBSR in improving asthma control. *Hypothesis: Asthma control and symptoms as assessed by the Asthma Control Questionnaire[3] will improve significantly more in MBSR than in HLC participants at 18 month follow-up.*

1.2 Secondary Objectives are to evaluate:

1) Asthma-related QoL. *Hypothesis: Asthma-related QoL (AQoL)[4] will improve more in MBSR than HLC participants from baseline to 18-month follow-up.*

2) Respiratory interoceptive accuracy and its mediating effect on asthma control, QoL, and medication use. *Hypotheses: MBSR will result in improved accuracy (Breath Perception Discrimination Test) at 6-, 12- and 18-months compared with HLC, and will be correlated with improved asthma control, QoL, and medication use.*

3) Lung function (change from baseline in 2-week average morning peak expiratory flow (PEF), spirometry (Forced Expiratory Volume in 1 second (FEV_1)) at 6-, 12- and 18-months compared with HLC. *Hypotheses: There will be no deterioration, and possibly improvement, in lung function in MBSR participants from baseline to 6-, 12- and 18-months as measured by PEF, or FEV_1 as compared with HLC.*

4) Cost-effectiveness in asthma control and management. Hypothesis: MBSR will be associated with improved cost-effectiveness and improved cost-utility by 18 months as compared with HLC. This will be based on clinical outcomes (e.g., asthma control, QoL, medication use) as well as quality-adjusted life years.

2. BACKGROUND AND RATIONALE FOR STUDY

2.1 Background on Asthma and the Role of Emotional Factors

Asthma is a common chronic disease affecting 7.3% (16.4 million) of U.S. adults[5] and costs $18.3 billion annually in direct healthcare costs and lost productivity.[6] Accurate patient self-management of symptoms is critical in asthma clinical care.[7, 8] This includes: accurate symptom monitoring; self-administering rescue medication when it is felt necessary; adherence to medication regimen; medical monitoring; and sometimes, adjustments to life activities.

Emotional factors have long been known to adversely affect asthma patients' everyday recognition and experience of their symptoms: The sub-clinical mental distress prevalent among asthmatics is associated with over-perceiving dyspnea and self-reported respiratory and asthma symptoms that are not accompanied by objective spirometry measures.[9-18] This results in frequent and costly self-management errors from increased reports of asthma symptoms, and unnecessary use of rescue medication. Downstream effects are poorer asthma control, physical health, more frequent emergency room and medical service trips, worse QoL, and asthma deaths in extreme cases.[19-24]

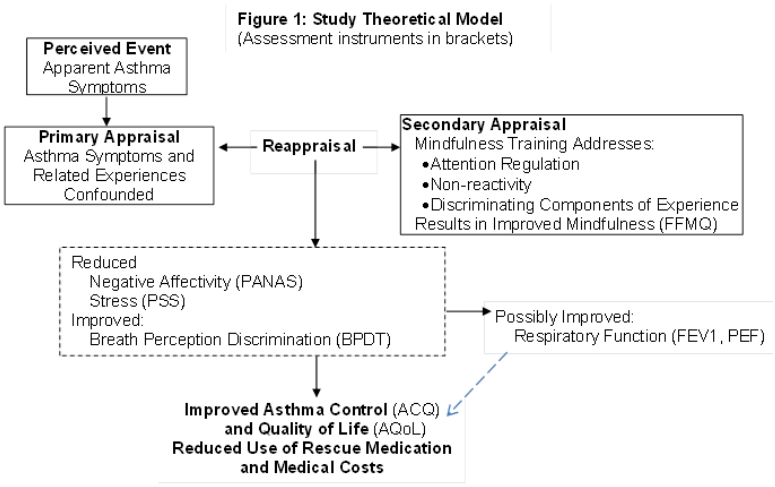
Programs that facilitate adjustment to asthma are clinically important for increasing QoL[25-28] even when lung function does not improve as a result.[29] But despite the importance of recognizing and coping with emotional factors in accurate symptom recognition for asthma control, self-management programs have not addressed these factors; rather they have focused on education about triggers and medication usage.[30] A Cochrane review of psychological interventions[31] found no firm conclusions could be drawn as to their benefit. And while 40% of asthma patients use some form of complementary and alternative medicine (CAM),[32] such as biofeedback,[33, 34] relaxation,[35] and breathing exercises/yoga,[36] these have focused on improving respiratory function and symptoms and QoL outcomes have been inconclusive and/or limited by study design.[32, 36-38]

Educating asthma patients to recognize and better cope with emotional factors affecting their symptom management has the potential to significantly improve asthma control, with downstream effects on QoL and asthma health care costs.

2.2 Rationale for Mindfulness Training in Asthma Control and Pilot Findings

Patients' capacity to discriminate between asthma-related dyspnea and the impression of breathlessness, choking sensations and chest tightness due to situational anxiety and stress[11, 24, 39] is very important for making sound self-management decisions. But elevated distress is related to low interoceptive accuracy[40] and a

portion of the low congruence between spirometry and patients' symptom reports may be attributed to difficulty in distinguishing symptoms of anxiety or stress from those due to asthma;[12-14]



Mindfulness involves learning to pay attention to bodily sensations, distinguishing these from associated thoughts and feelings, and cultivating a non-reactive awareness of the experience.[41 42] Stable awareness facilitates adaptive symptom appraisal[41, 43-46] as thoughts and feelings no longer threaten to overwhelm,[47-49] enabling self-regulatory behavior[50] in the face of distressing conditions.[43, 44, 51] Importantly, MT is associated with increased perceptual accuracy,[52-54] increased bodily awareness, and reduced affective negativity and disease-related stress/distress,[43, 44, 55-58] and recent findings by one of our group (CK) show that MT is associated with enhanced accuracy in breath discrimination thresholds,[59] and the mindfulness body scan decreased the tendency to mistakenly report the presence of tactile sensation in absence of a stimulus.[60] Would MT improve asthma patients' accuracy in discriminating asthma symptoms from the distressing cognitions and affect related to the sensations and external factors such as symptom triggers[24, 61] and, in turn, reduce the tendency to mistakenly label the experience of affective distress as a physical, asthma-related symptom?

MBSR is an eight week MT program that has been shown to increase mindfulness,[62, 63] decrease perceived stress,[62] increase resilience,[64] and support coping with a wide range of difficult emotional situations and symptom-related challenges, and is available in over 200 locations.[51, 55, 65-68] Furthermore, there are minimal risks associated with participation. As such, it seemed a promising intervention to reduce the distress associated with asthma by supporting patients in responding more appropriately to their symptoms and so prevent symptom exacerbation with downstream effects on asthma control and QoL.

The theoretical framework is informed by Lazarus and Folkman's transactional model in which perception of stressful situations is a transactional process of the person's cognitive-emotional appraisal of a situation in relation to their perceived coping resources to address the situation.[69] Appraisal is posited to take place in two stages. In primary appraisal, the person evaluates the situation as being irrelevant, benign, or stressful to their well-being. Secondary appraisal pertains to the person's perceived coping skills to manage the situation. An iterative process takes place over time in which secondary appraisals feedback upon primary appraisals, modulating the degree of stress experienced.

Mindfulness training is hypothesized to impact secondary appraisal of asthma symptoms and related components of the experience. Figure 1 illustrates that in the primary appraisal the patient may not clearly distinguish between respiratory symptoms and related stressful thoughts and feelings, increasing the possibility of less accurate perception of respiratory symptoms. The increased alertness to physical sensations that derives from exercises such as the body scan and the resultant capacity to distinguish physical symptoms from the symptom-related thoughts and feelings, together with the non-reactivity that is cultivated, makes possible a secondary appraisal[45].

The resultant reappraisal may result in improved asthma control through one or more of several avenues: (1) The patient will more accurately discriminate between their asthma symptoms and their emotional reactions associated with the experience and so is more clinically accurate; (2) The more accurate perception of symptoms may lead patients to better adherence of their medications, especially with regard to slowly acting inhaled corticosteroids; (3) Patients will better know, in a more timely fashion, when to seek medical help to adjust their therapy; and (4) Better perceptual accuracy and a more discriminating, objective self-assessment of symptoms may make patients more aware of their asthma triggers and lead them to better avoid stimuli that worsen airway inflammation and bronchospasm.

Following a successful feasibility study, an exploratory pilot study[70] (R21AT002938; Multiple PIs: Pbert and Carmody; Co-Investigator: Madison; 2006-2009) recruited 84 patients from UMMHC primary care and pulmonary care clinics with mild, moderate or severe asthma who were randomized to MBSR or an

educational Healthy Living Course (HLC) control program matched for frequency, duration, and group format/support. Assessments were at baseline, 10 weeks (post-intervention), and 6- and 12-month follow-up.

*Asthma-related Quality of Life (*Asthma QoL Questionnaire (AQoL): Overall QoL (p=0.001) and three of the four component scores of the AQoL: activity limitations (0.57, p=0.005), asthma symptoms (0.46, p=0.009), and emotional function (0.63, p=0.002) significantly improved at 12-months in MBSR compared to controls. The intervention effects (0.55, 5.34 to 5.97 at 12 months) greater than 0.5, indicated a clinically significant improvement.[71] At 12 months, 34% of MBSR participants had a QoL change of 1.0 (moderate increase[71]) or greater, compared to 12% in HLC (p=0.02). And 18% had large improvements ($\geq$ 1.5 points) compared to 5% in HLC (p=0.080).[71] These results were comparable to QoL improvements in patients with mild to severe asthma in trials of an inhaled corticosteroid (Ciclesonide),[72, 73] a 5-lipoxygenase inhibitor (Zileuton),[74] and an anti-IgE antibody in patients with severe allergic asthma.[75]

Lung Function: MBSR had no effect on lung function (Change from baseline in 2-week average morning peak expiratory flow (PEF), PEF variability, and FEV_1).

Asthma Symptoms (Symptoms Subscale of the AQoL) improved significantly in MBSR at 12 months compared to controls (AQoL Symptom subscale; intervention effect 0.46, p=0.009). Further, the MBSR arm were using their short-term rescue medication less frequently than the controls (p=.001).

Asthma Control (2007 NIH/NHLBI guidelines): The percentage of MBSR patients classified as well-controlled asthma[76, 77] went from 7.3% at baseline to 19.4% at 12 months, compared to 7.5% to 7.9% of controls. While this was not a statistically significant difference between arms over the entire follow-up period (p=0.132), the pilot was not powered to detect changes in asthma control.

The improvements in asthma symptoms and improving trends in asthma control coupled with lung function data indicating no change over time, argue that MRSR did not adversely lead to poorer "control" through decreased adherence to medications or failure to recognize deteriorating respiratory status. Rather, these findings provide preliminary data suggesting that MBSR may have a beneficial effect on asthma control as assessed by the new guidelines for classification of asthma control that include asthma symptoms.[1]

Stress/Distress: The mean baseline MBSR Perceived Stress Scale (PSS) score (17.3) was at the 75th percentile for a U.S. normative sample, confirming the prevalence of elevated stress/distress in asthma patients.[9, 11, 78, 79]. [80] At 12 months, MBSR had improved to the U.S. norm (13.0) while controls remained unchanged (15.8 to 16.0) (between arm differences at 12 months p=0.001).

The sample mean anxiety score (Hospital Anxiety and Depression Scale (HADS) at baseline (7.17) was at the 62nd percentile for a non-clinical normative female sample (the sample was 70% female).[81] At 12 months there was a significant difference between arms on reductions in anxiety (p=0.045), and MBSR anxiety scores had improved to the 44th percentile. While these are sub-clinical levels of distress, we note that the sub-clinical stress/distress prevalent among asthmatics[9, 11] is associated with worse asthma control and QoL.[22]

Biomarkers of Airway Inflammation: A supplemental study to the pilot examined serum IFN-γ, IL-4, circulating regulatory Tcells, and IgE levels as indicators of changes in airway inflammation. Blood was drawn at each time point and assayed using flow cytommetry. No effects were found with these specific biomarkers and so we have not included them in the present study.

In summary: Our pilot study allowed us to: 1) Develop an innovative and credible active control program (HLC) that matched MBSR for non-specifics; 2) Refine our study procedures; 3) Demonstrate our ability to successfully recruit and retain asthmatics into an RCT and complete data collection with high fidelity; and 4) Obtain preliminary data on the effect of MBSR that showed clinically significant improvements over 12 months in asthma-related QoL, asthma symptoms and reduced use of rescue medication, and important improvements in stress and distress, even in the absence of improvements in lung function.[17, 18] Enduring improvements in asthmatics' QoL to this clinically significant degree would make a great public health impact.

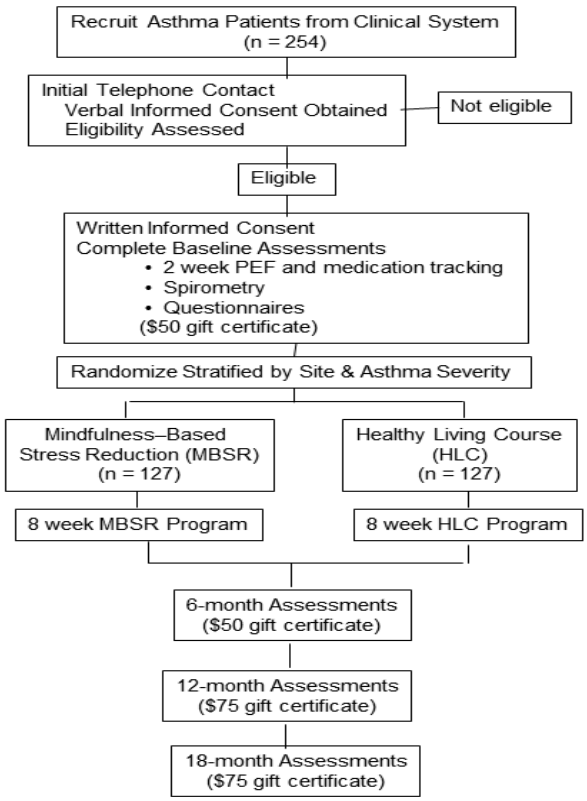
3. THE STUDY DESIGN

The primary goal of the 5-year RCT is to evaluate the effect of MBSR on asthma symptom management as reflected in level of asthma control at 18-month follow-up. Secondary goals include examining the effects of MBSR on asthma-related QoL, perceptual accuracy of dyspnea and its mediating effect on asthma control and management, lung function, and medication use; and the cost-effectiveness of MBSR in asthma control. Two hundred and fifty four patients 18 years and older with documented mild, moderate or severe asthma[1, 2] will be recruited from the patient population of UMass Memorial Health Care (UMMHC) and the Miriam Hospital. Data

is expected on 216 participants at study completion. Participants will be randomly assigned to Mindfulness-Based Stress Reduction (MBSR), in which they will attend the 8-week program, or a Healthy Living Course (HLC) control condition, in which they will attend an 8-week program consisting of lectures and discussion on health-related topics. Randomization will be done by the data manager at UMMS, and be stratified by site, and asthma severity with each stratum in randomly allocated blocks of two using the ralloc program in Stata.[82, 83]

Participants will be recruited into the study in 13 cohorts over 13 quarters to coordinate with the ongoing University of Massachusetts Medical School (UMMS) and Miriam MBSR programs, and to maximize the potential pool of recruits. Assessments will be at baseline, and 6- 12-, and 18-months post-baseline. The timeline allows sufficient time for study participant recruitment and follow-up to address the study's specific aims. See Figure 3 Study Design below. All study personnel will be blind to intervention assignment except those involved with randomization codes, delivery of the interventions, and preparation of reports for the

Figure 3. Study Design



independent monitoring. These unblinded staff will have no access to the data, no influence on the outcome assessments, and no involvement in data analysis.

4. SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

4.1 Inclusion Criteria: To be included in the study, patients must meet the following criteria:

- Age 18 and older
- Diagnosis of asthma for greater than 12 months documented by a pulmonologist or board-certified allergist; or diagnosis of asthma for greater than 12 months documented by another type of provider that also includes an objective indicator of bronchial hyper-responsiveness (positive methacholine challenge test or $\geq$ 12% improvement in FEV_1 or FVC in response to bronchodilator);
- Meets criteria for mild, moderate or severe asthma; [1, 2]
- Treatment with inhaled corticosteroids for at least 3 months with stable dosing for greater than 1 month;
- Able to read and understand English, and complete informed consent process and study data collection procedures.

4.2 Exclusion Criteria: Candidates meeting any of the following will be excluded from study participation:

- Currently smoking combustible tobacco, or smoked combustible tobacco in the past year;
- Other lung diseases besides asthma (e.g., pulmonary hypertension, cystic fibrosis, COPD-emphysema, bronchiectasis, chronic bronchitis, lung cancer);
- Unable to undergo spirometry;
- Active cancer, except non-melanoma skin cancer; Currently receiving treatment for symptomatic cardiovascular disease (including congestive heart failure, unstable angina, have chest pain or had myocardial infarction or heart attack within past 6 months);
- Current or recent (within the past 3 months) severe exacerbation of asthma requiring hospitalization or oral glucocorticoids;
- Currently pregnant or planning to become pregnant in the next 18 months (due to change in asthma course and confounding effects of physiologic gestational dyspnea on symptoms);
- Hospitalized for a psychiatric or mental health concern in the last 2 years;
- Has taken the MBSR program in the past, and/or currently practicing meditation, or yoga that includes a meditative component, at least weekly for the past 2-3 months.

4.3 Study Enrollment Procedures

Study population: We will recruit 254 participants from the pool of patients at the UMass Memorial Health Care (UMMHC) and Miriam Hospital to provide a total of 216 patients at 18-month follow-up. UMMHC is the clinical partner of UMMS and the largest health care system in Central and Western Massachusetts. There are 17 pulmonologists in the Lung and Allergy Center, and approximately 3,510 patients (Caucasian 78%, non-Caucasian 22%) with a diagnosis of asthma and prescribed an inhaled steroid. UMMS has experience through the NIH-funded pilot study in successfully recruiting patients with asthma into a randomized controlled trial. Miriam Hospital is part of the Lifespan Corporation and is the largest healthcare provider in the state of Rhode Island; their asthma clinic is a critical tertiary asthma clinic that serves the entire state. The network has 37 pulmonologists on staff and 2,778 outpatients with a clinical diagnosis of asthma (Caucasian 68%, non-Caucasian 32%). The respiratory therapist on this team has been involved with recruitment and education in asthma research, and is currently involved with other research projects.

Recruitment procedures: Participants will be recruited to 13 cohorts over 13 quarter periods, with roughly 10-11 participants per cohort. While minor adaptations to the recruitment protocol will be made to cater to institutional arrangements at each site, recruitment procedures will be similar to the successful procedures used in the pilot. The Project Director, Ms. Susan Druker, will oversee recruitment at both sites.

Potentially eligible participants (documented diagnosis of asthma) per medical record from most recent visit scheduled for a clinic visit will be identified through the practice's office scheduling and medical record system (e.g., IDX and Allscripts/Epic). The Project Director/Research Assistant (RA) will email the pulmonologist with the identified participant and time of their appointment, and place a purple study sheet in the patient's file that contains information about the study. The Miriam site will speak directly with the provider or medical assistant about the potential subject. The RA will be present in the clinic on the day of the patient's visit and, if the pulmonologist/provider considers the patient to be a suitable candidate for the study, and the patient expresses interest in participating or learning more about the study, the pulmonologist/provider will invite the Research Assistant into the examination room to screen the patient for eligibility. It will be explained that the patient's overall care at their hospital will in no way be affected by whether or not the patient participates in the study. If the RA is not able to be in the clinic on the day of the patient's visit, the provider will ask the patient to sign a consent to contact form so the RA may call at a later time to explain the study, and obtain verbal informed consent to conduct the eligibility screening. If the patient is eligible, the RA schedules a consent/intake visit with them (See *Telephone eligibility screen interview* section below). Ms. Druker the Project Director will supervise the RA to maintain consistent delivery.

If a participant is not referred, the pulmonologist/provider will complete a form providing the reason (too busy to discuss, participant did not show up for appointment, participant not eligible, participant not interested)

A list of active patients (i.e. seen in the Primary Care, Family Medicine or Pulmonary Clinics for a continuity (not urgent care) visit within the past 2 years) with a documented diagnosis of asthma on their problem list and an inhaled steroid on their medication list will be generated using the MICARD automatic medical record system described above. We will also contact the Mass Lung & Allergy, PC located in Central Massachusetts to refer eligible study patients. These referrals will be done through the same process as

described above (e.g., purple sheet, in clinic recruitment or via letter). We also will recruit via newspaper ads and on-line.

At Miriam this report will be generated via EPIC LifeChart, the site's electronic medical record system. Miriam will also reach out to pulmonary practices in the community for referral of asthma patients. The study coordinator/RA will be contacted by the doctors if a potential subject is scheduled to be seen. The doctor will present the study to the patient, and if interested, the patient will sign a permission to contact form and the RA will follow up via phone to discuss the study and screen for eligibility or will be seen by the RA in the clinic.

As in our prior studies, a HIPAA waiver authorization will be requested from our Institutional Review Board prior to obtaining the list of patients. Exclusion and inclusion criteria also will be included in this search. At the UMMS site only, each physician will receive a spreadsheet of their patients' names and asked to cross off anyone who s/he does not feel would be appropriate to participate in the study. At Miriam, providers will not review a spreadsheet; rather, the report generated by EPIC/LifeChart will be used as a mailing list. A form letter signed by the physician and the Principal Investigator, and containing a stamped envelope, will be sent to each patient inviting them to participate. The patient will be asked to indicate if s/he is: (1) interested in participating, or (2) not interested in participating. All patients responding with 1 will be called.

We will also be reaching out to Conquering Diseases, a database of individuals who are interested in participating in research studies at both UMMS and Miriam. They will provide us a list of patients who have asthma and are interested in participating in the study. The RA will then email or call those patients.

Consent/Baseline visit, written informed consent, baseline assessments and randomization: Section 11.2 contains details of the orientation and informed consent procedures. The RA will schedule an in-person consent/baseline visit for eligible persons at the study offices at that site at which they will be given further opportunity to ask, and have answered, any remaining questions they may have about their participation. If they still wish to enroll in the trial, they will complete the written informed consent document. After providing written consent they will complete the baseline assessments. After all baseline assessments are completed, participants will be randomly assigned to one of the two study arms.

Based on our experience with the pilot study, we also will utilize proactive strategies to improve recruitment and reduce refusal rates, including: (1) working with physicians and nurses to assist in active recruitment of their patients, (2) providing patients with a clear explanation of the study and participation requirements, (3) brainstorm strategies with Chief Pulmonologists.

Telephone eligibility screen interview: Interested patients will be called by the Research Assistant (RA) at each site to establish eligibility, explain the study in detail and seek verbal informed consent. Using a script and screening form to standardize this phase of enrollment, the RA will explain the need to collect some information from the patient to determine whether they are eligible to participate and request verbal permission to proceed. It will be explained that the patient's overall care at their hospital will in no way be affected by whether or not the patient participates in the study. Upon obtaining verbal consent the RA will complete the phone screen which will include questions related to the eligibility criteria. Ms. Druker the Project Director will supervise the RA to maintain consistent delivery of the orientation sessions.

Consent/Baseline visit, written informed consent, baseline assessments and randomization: Section 11.2 contains details of the orientation and informed consent procedures. The RA will schedule an in-person consent/baseline visit for eligible persons at the study offices at that site at which they will be given further opportunity to ask, and have answered, any remaining questions they may have about their participation. If they still wish to enroll in the trial, they will complete the written informed consent document. After providing written consent they will complete the baseline assessments. After all baseline assessments are completed, participants will be randomly assigned to one of the two study arms.

Randomization will be stratified by site and asthma severity with each stratum in randomly allocated blocks of two using the ralloc program in Stata.[82, 83] The RA will generate the random allocation sequence, will communicate randomization status to each participant at time of randomization and the allocation table will be uploaded to the RedCap database. Participants in each cohort will be randomized altogether and sent to the same MBSR and HLC classes. This approach is necessary to ensure that the seasonality and temporal differences be balanced between the two arms. We anticipate participants will begin their intervention (MBSR or HLC) within 8 weeks of randomization. Reasons for ineligibility and for non-participation of eligible candidates will be documented through the use of a Screening Form completed by the RA. Data will be collected from all patients who provide consent to be screened but who were found to be ineligible at screening and for those found to be eligible but deciding not to not participate.

Supporting Participant Attendance at Intervention Classes: At the time of recruitment and enrollment, the RA will emphasize the importance of attending the intervention classes and ask participants if they are planning to be absent for more than one class for the upcoming cycle. If so, they will be advised to enroll in the following cycle of intervention classes. The MBSR program requires attendance at an orientation session prior to the first class, therefore the RA will call participants randomized to MBSR two days before the orientation to remind them to attend. In the two days prior to the initial MBSR and HLC classes, the RA will call all study participants to remind them that their program is starting, reiterate that they are required to attend the intervention sessions, and problem solve any challenges the participant anticipates about intervention class attendance.

To support ongoing class attendance in the MBSR arm, in addition to the call made by MBSR instructors when a person misses a class, the RA will check the MBSR attendance information for each class to check study participants' attendance for each week's classes. The RA will follow-up with a call to those study participants who have missed that class to identify barriers to participation and brainstorm strategies for attending the MBSR classes to enhance intervention adherence.

To support ongoing class attendance in the HLC arm, the HLC instructors will email the RA with the attendance list for that week's classes. The RA will follow-up with a call to those study participants who have missed that class to identify barriers to participation and brainstorm strategies for attending the HLC classes to enhance intervention adherence.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

Intervention condition (MBSR): The Mindfulness-Based Stress Reduction (MBSR) program consists of 8 weekly group sessions of 2 ½ hours duration, plus an all-day class on a weekend day during the 6th week.[84] Classes include systematic and intensive training in mindfulness and its application to everyday life, and the range of challenges arising from chronic diseases, chronic pain conditions, and life stresses of the participants. Formal training in mindfulness is through: (a) body scan, a gradual moving of attention through the body accompanied by awareness of breathing and other bodily sensations while in a lying position, (b) sitting meditation, focusing on the awareness of breathing, bodily sensations, thoughts, and feelings, practiced sitting upright on a chair or cushion, and (c) mindful stretching exercises practiced with awareness of breathing, intended to develop mindfulness during movement. Group exercises and interactions focus on the challenges and achievements that participants experience in integrating mindfulness into their lives and the stressful situations they encounter.

Throughout the 8-week program participants are asked to do up to 45 minutes of home formal meditative-practice-related practice each day, and supported in generalizing skills developed in this way by informal practice. This consists of bringing self-observations and the moment-to-moment non-judgmental awareness into neutral everyday experiences and daily life, and eventually, stressful activities.

The MBSR programs have similar formats, facilities, and structure across the two study sites, UMMS and Miriam Hospital. Miriam Hospital site instructor, Dr. Ellen Flynn, follows the established format in the MBSR program and treatment manual developed and validated by the Center for Mindfulness (CFM), University of Massachusetts School of Medicine. Participants in the MBSR courses at each site will include community members and asthma patients. Group size will be 20-25 participants.

Structure: Throughout the duration of the trial, asthma patients will be offered two different scheduling options as classes will be offered twice-weekly by Dr. Flynn (as well as a substitute teacher). During the course of the active portion of the study, there will be 13 cohorts over 13 quarters.

Facilities: MBSR classes at the UMass site will be held in the usual MBSR classroom in the Center for Mindfulness. The Miriam Hospital MBSR program will be held at the Lifespan Women's Medicine Collaborative West River facility or in the generously appointed mind-body room (720 sf) at the Lifespan-Miriam Hospital's Collyer Street facility, both located in Providence. Subjects will be given detailed directions to the appropriate facility. Classrooms at either location can accommodate up to 25 patients.

Teacher qualifications: Classes at the UMass site will be taught by the regular CFM MBSR instructors. Dr. Flynn at the Miriam site has taught mindfulness for over ten years and has broad experience with a wide-array of patient populations in mindfulness. She has received the basic and advanced MBSR certifications from the UMass Center for Mindfulness. Eric Loucks will be a "back-up" teacher who will offer 1-2 trainings per year.

She is similarly qualified with over 8 years of experience teaching mindfulness and with basic and advanced certifications from the UMass Center for Mindfulness.

Control condition (HLC): The Healthy Living Course (HLC) consists of 8 weekly group sessions of 2 ½ hour lectures and discussions about health-related topics. This condition controls for the 8-week contact, attention, group support, and other non-MBSR-specific factors that may contribute to its effectiveness. HLC participants in the pilot study reported on the 12-month assessment survey that the HLC was a face-valid and credible program. The HLC will be offered to community members (regardless of whether or not they have asthma) in addition to study participants, consistent with the mix of participants in the MBSR program. As they did successfully in the pilot trial, UMMHC's Marketing and Communications Department will advertise the course and recruit participants from the community. Lectures will be delivered by Health Educators, HLC topics include: healthy nutrition, physical activity/fitness, coping with stress (not including mindfulness), how to get a good night sleep, balancing work and personal life, your communication style, and living a drug-free life (smoking, alcohol, other drugs). Participants will be asked to complete daily assignments taking up to 45 minutes/day to complete related to the topic of each class (e.g., monitoring their diet and physical activity, noting barriers and facilitators) to match for MBSR homework.

The Healthy Living Course to be administered at the Miriam Hospital Collyer Street facility or The Lifespan Women's Medicine Collaborative is matched to the MBSR training in terms of its schedule and structure (e.g., 8 weeks of training sessions, with each session lasting 2.5 hours). Classes will follow the same instruction manual and curriculum at the UMass site and offer lectures and discussions about health-related topics.

Courses will be delivered by Miriam Hospital Health Educators.

5.2 Handling of Study Interventions

Following randomization, MBSR and HLC participants will begin in the next available program group. The time period between randomization and beginning the group program will be no longer than 8 weeks. Along with other non-study participant attendees, they will attend the 8 weekly 2½-hour classes, plus an all-day class on a weekend day during the 6th week. In response to NCCAM's call for trials of interventions whose results are generalizable to the wider population, and consistent with the pilot study, MBSR and HLC programs will be open to the community, not just consented participants. While we will track the proportion of study vs. non-study participants in each of the MBSR and HLC classes, we are unable to collect data from the non-study participants as they will not be consented.

At UMMS, MBSR classes will be conducted by the Center for Mindfulness (CFM) MBSR instructors, and at Miriam Hospital by Dr. Elizabeth Flynn. Instructors at both sites have at least five years of experience in delivering MBSR and have completed a professional graduate degree in a health related field. The HLC classes will be taught by certified Health Educators or Registered Dieticians at both sites.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions: Participants will be allowed to continue all medications and follow all behavioral recommendations prescribed by their health care providers with the exception of participation in non-study-related MBSR programs, meditation or yoga. Both controller and reliever medication use will be documented daily during the 2-week assessment period at baseline, 6-, 12-, and 18 months. In addition, controller medication dose and frequency of use will be obtained from electronic prescription data (see section 6.2. below).

5.3.2 Required Interventions: Participants will be randomly assigned to attend either the MBSR program or the HLC program described in section 5.1. These programs include participation in 8 weekly 2½-hour classes, an all-day session, and completion of homework assignments.

5.3.3 Prohibited Interventions: In order not to confound the intervention effects, past participation in an MBSR program or currently practicing meditation or yoga on a regular basis is an exclusion criterion. In addition, participants will be asked to refrain from participating in any MBSR program and/or practicing meditation or yoga on a regular basis outside of their study participation over the course of the trial.

All concomitant interventions will be recorded at each time point

5.4 Adherence Assessment

To assess adherence to the interventions the number of MBSR and HLC classes attended will be documented by instructors delivering the MBSR and HLC classes. Completion of homework during intervention will be assessed by participants completing homework logs that will be collected each week. MBSR

participants will record number of minutes of homework they do each day using the homework logs[62]. HLC participants will record their completion of weekly assignments. During follow up, MBSR participants will estimate the usual minutes of mindfulness practice they have been doing each week in the interval since their last assessment. Instructors will not see the completed logs which participants will place in a locked box in the classroom and which will be collected by the RA.

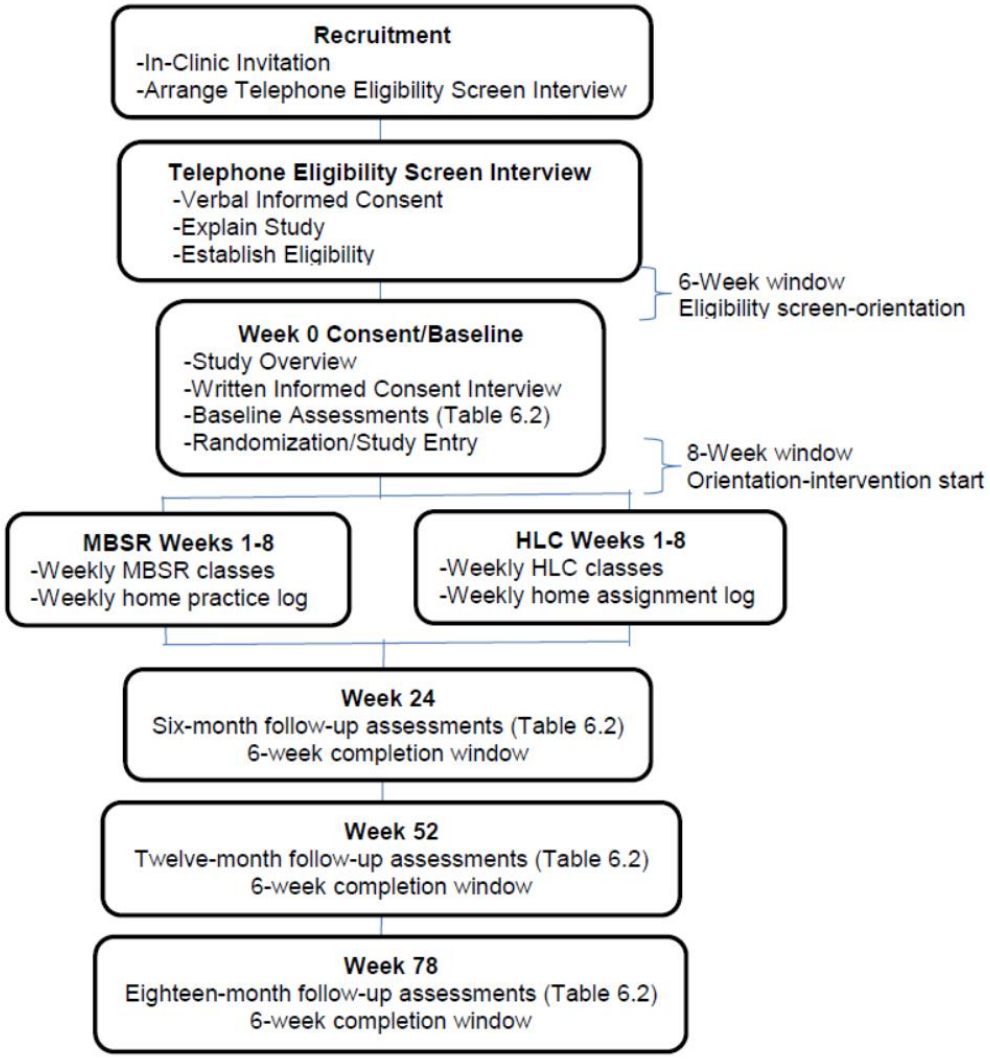
Based on the average number of classes attended, and homework completed, in the pilot trial, a protocol deviation will be considered to have occurred when a participant has attended less than five of the nine classes, and not completed the homework for those classes. Because MBSR and HLC programs will be open to the community, not just consented participants, we will not have permission from all attendees and are unable to record these programs. Fidelity to MBSR protocol will be ensured through ongoing weekly supervision meetings currently conducted with UMass Center for Mindfulness MBSR instructors in which curriculum delivery is reviewed and potential threats to fidelity are discussed. MBSR instructors at the Miriam Hospital site will participate in these weekly supervision meetings in person or via Skype to ensure fidelity and standardization across the two sites. Fidelity to HLC protocol by HLC instructors and standardization at both UMMS and Miriam sites will be ensured through weekly supervisory meetings held by Dr. Pbert, in which curriculum delivery is reviewed and potential threats to fidelity are discussed.

6. STUDY PROCEDURES

6.1 Participant Flow and Evaluation Time Points

The flow of participants through the study and the points at which evaluations occur is illustrated in Figure 6

Figure 6: Participant Flow and Evaluation Time Points



6.2 Description of Evaluations and Schedule

Each of the study evaluations are described in the following table, together with time point at which they are administered.

Construct/Function	Measures	Evaluation Time Points			
Primary Outcome		**BL**	**6m**	**12m**	**18m**
Asthma Control	Asthma Control Questionnaire (ACQ) [3] is a validated 7-item multi-component measure that assesses the 5 asthma symptoms considered most important and most used by clinicians for evaluating asthma control, along with use of short-acting beta-agonist and FEV_1 percent predicted. Patients recall their symptoms and short-acting beta-agonist use during the previous week; FEV_1 is obtained from spirometry. Questions are scored on a 7-point scale (0=good control, 6=poor control), and the overall score (range 0-6) is the mean of the seven responses. Changes of 0.5 or greater in the score are considered important differences.[85]	■	■	■	■
Secondary Endpoints					
Symptoms, Symptom-free days	Asthma Control Diary[3] completed daily for 2 weeks at each assessment point provides daily asthma symptoms and the proportion of symptom-free days per week. For comparison to the ACQ results, diary information will be combined with lung function data in order to categorize the level of asthma control according to 2012 GINA guidelines, with the categorical variables being controlled, partly controlled, and uncontrolled.	■	■	■	■
Medication Use	Both controller and reliever medication use will be documented daily during the 2-week assessment period. In addition, controller medication	■	■	■	■

	dose and frequency of use will be obtained from electronic prescription data. Prescription fills will be identified through pharmacy claims data as described in prior studies.[86] These data identified more than 99% of all inhaled corticosteroids (ICS) prescriptions filled by health plan members.[87] Adherence is estimated as the number of days' supply for each fill divided by the total number of days between the present fill and the subsequent ICS fill. Periodic adherence estimates will be assessed and a final overall mean measure of adherence is then calculated based on the percentage of ICS adherence for each interval.				
Quality of life	Asthma Quality of Life Questionnaire (AQoL)[4] has 32 items assessing impairment in 4 areas of function shown to be important to the QoL of adult patients with asthma (activity limitations, asthma symptoms, emotional function and environmental exposure). Overall QoL is computed by averaging scores on the 4 domains. Items assess the degree to which important activities have been limited by asthma during the last 2 weeks on a 7-point scale (1= maximal impairment, 7= no impairment). Shown to be valid, reliable and sufficiently sensitive to changes in asthma symptoms to capture the effects of an intervention in a clinical trial.[4, 88] Changes in scores of 0.5 or above represent clinically meaningful improvement in QoL.	■	■	■	■
Respiratory Interoceptive Accuracy (RIA)	The Breath Perception Discrimination Test (BPDT) measures ability to detect small changes in resistive load. This test will be done in the Pulmonary Diagnostic Laboratory at each site and follow procedures outlined in Dr. Catherine Kerr's recent publication.[59] The test begins with a brief training period to familiarize participants with 5 resistive load settings (including 4 Hans Rudolph very-low-threshold calibrated resistors and 1 blank (no resistance) condition). During the test period, the presentation of the resistor is announced at the onset of a new inspiration for the duration of one full breath cycle. At the conclusion of the breath cycle, participants pause for 5 normal breaths, then the next resistor in the block is presented. The test will be divided into 6 blocks during which there is a random presentation of each resistor so that participants carry out 30 ratings (6 for each condition) over the course of the test. Time to complete: 30 minutes.	■	■	■	■
Exacerbations and Health Care Utilization/Cost	Number of moderate and severe exacerbation, asthma-related regularly scheduled office visits, acute care visits, hospitalizations, emergency room visits, need for intubation or mechanical ventilation, and other costs during the prior 6 months at baseline, 6-, 12- and 18-month follow-up and associated clinic and hospital costs will be determined by two methods: self-report, and actual hospital and health system costs (direct and indirect) obtained from administrative reimbursement data. Brief Treatment Cost Analysis Tool (TCAT), a validated costing tool for counseling interventions,[89] will be used to calculate cost of delivering MBSR and HLC.	■	■	■	■
Lung Function: Spirometry	Spirometry assesses the level of air flow limitation according to the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Measurement will be done in the site Pulmonary Diagnostic Laboratories according to American Thoracic Society guidelines before and after inhalation of bronchodilator.[90] This includes instructing participants to not take a bronchodilator at least 4 hours prior to their spirometry, and assessing lung function both before then 30 minutes after bronchodilator to assess best lung function and responsiveness to bronchodilator therapy. The team pulmonologist at each site will interpret all spirometry tests.	■	■	■	■
Lung Function: Peak Expiratory Flow (PEF)	Ambulatory recording of PEF provides an objective day-to-day measure of airway obstruction and is one of the most commonly-reported physiological outcome variables in clinical trials.[1] Participants will be provided a PEF meter and instructed to document PEF morning and evening for 2 weeks following each of the assessment time points. Data will be expressed as absolute values and as percent predicted. As indices of PEF variability, we will use diurnal and between-day variability.	■	■	■	■
Mindfulness	Five Facet Mindfulness Questionnaire (FFMQ)[91, 92] assesses the tendency to be mindful in everyday life through 15 items covering 5 facets of mindfulness: observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience. The scale items can be completed meaningfully by participants in both study	■	■	■	■

	conditions. Items are rated on a Likert scale from 1 (never or very rarely true) to 5 (very often or always true). FFMQ has been found to be valid and sensitive to change. [93] Alpha coefficients for the 5 facets range from .72 to .92. [91] FFMQ scores correlate with MT experience, predict decreases in psychological symptoms,[93] and mediate improvements in well-being in MBSR.[62]				
Perceived Stress	Perceived Stress Scale (PSS),[94] a well-validated 10-item scale based upon the transactional model,[69] measures degree to which situations in one's life over the past month are appraised as unpredictable, uncontrollable and overwhelming. A higher score indicates a greater degree of perceived stress, and lower scores are associated with better coping resources.[95] Higher PSS scores have been associated with failure to make health-promoting behavior changes.[96, 97] Participation in MBSR has been associated with significant declines in PSS scores. [98]	■	■	■	■
Moderating/Process Variables					
Sociodemographic Variables	Age, gender, race/ethnicity, years with asthma diagnosis, number of years taking asthma medication, body mass index, education level, marital status, employment status.	■			
Medical and Psychiatric History	Focused medical history, comorbid medical conditions, medications, smoking status, physician and ER visits, hospitalizations, and focused psychiatric history	■	■	■	■
Adherence to MBSR and HLC Requirements	Number of MBSR and HLC classes attended will be documented by instructors delivering the MBSR and HLC classes. Completion of homework during intervention will be assessed by participants recording number of minutes of home practice they do each day using homework logs.[62] During follow up, MBSR participants will estimate the usual minutes of mindfulness practice they have been doing each week in the interval since their last assessment. Participants who attended four or fewer intervention classes will be asked their reasons for non-attendance		■	■	■
MBSR and HLC Fidelity	MBSR instructors at both sites will participate in the ongoing weekly supervision meetings conducted with UMass Center for Mindfulness MBSR instructors to ensure fidelity to MBSR protocol. HLC instructors at both UMMS and Miriam will have weekly supervisory meetings with Dr. Pbert in which curriculum delivery is reviewed and potential threats to fidelity are discussed.				
Days of Work/School Missed	Self-report of number of days of work or school missed because of asthma in the 6 months prior to each assessment.	■	■	■	■
Triggers/Seasonal Variability	Self-report from list of 11 common asthma triggers (e.g. aspirin, cold air, infections etc.), and the months of the year their asthma is worse	■	■	■	■
Confounding Effects	A Confounding Effects Inventory (CEI) developed in our pilot study documents common confounding effects experienced in the past 6 months that could impact asthma control. These include environmental confounders in the home (moved, changes in active or passive smoking, pets), workplace, and social environments; medical problems (sinus infections, upper and lower respiratory tract infections, other infections, gastroesophogeal reflux disease, surgery, and new diagnosis or change in status of other cardiovascular or respiratory conditions); changes in asthma and other medications; and changes in health insurance coverage.	■	■	■	■
CAM Use for Asthma/Concomitant Interventions	Self-report of CAM treatments for asthma (e.g. acupuncture, homeopathy, herbal medicine, prayer, supplements, dietary restrictions) in the 6 months prior to each assessment.	■	■	■	■

6.2.1. Screening Evaluation: Upon obtaining verbal consent the RA will complete the eligibility screen which will include questions related to the eligibility criteria using a script and screening form to standardize this phase of enrollment. Criteria for eligibility (inclusion and exclusion criteria) are listed in sections 4.1 and 4.2. A 6-week range will be allowed prior to study entry during which all screening evaluations to determine eligibility will be completed.

6.2.2. Participant Consent, Study Enrolment, Baseline Assessment and Randomization: Eligible persons will attend an orientation session on the day of their clinic visit or, if the RA was not able to be at the clinic on the day of their visit, at the study offices at that site during which the site RA will explain in full detail the study goals and procedures so as to familiarize the patient with what to expect, and what is expected from their participation in both the interventions and the assessments. Subjects will be informed about all of the risks

described above and all aspects of the study, and emphasize that their participation is voluntary and that they may withdraw at any time by contacting the RA and/or the contact PI. Contact information for the RA and the PI, as well as the IRB (for complaints) is contained in the consent form.

Participants will be given ample opportunity to ask questions before giving their consent and all of the potential subject's questions will be answered. While the consent process is expected to take 20-30 minutes, we will minimize the possibility of coercion or influence by providing subjects up to one hour to decide about participation and ample opportunity to reconsider their decision. They will have the opportunity to opt out at the interview or at any point on the study day, including while the study is underway.

The RA conducting the process will determine that the subject understands the information provided and is capable of making and communicating an informed consent. If they still wish to enroll they will complete the written informed consent document (contained in a separate document from this protocol).

Copies of the signed consent form and HIPAA document are retained by the participant and the Project Director. The date of signing will be considered their study enrollment date. This date will be recorded on the study participant's case report form. Forms will be kept in locked filing cabinets separate from all data. All individuals responsible for obtaining consent will have up to date CITI training.

After providing written consent participants will complete the baseline assessments described in Table 6.2.

After all baseline assessments are completed, participants will be randomly assigned to one of the two study arms. Randomization will be stratified by site and asthma severity (see table below) with each stratum in randomly allocated blocks of two using the ralloc program in Stata.[82, 83] The RA will generate the random allocation sequence, will communicate randomization status to each participant at time of randomization and the allocation table will be uploaded to the RedCap database. Participants in each cohort will be randomized altogether and sent to the same MBSR and HLC classes. This approach is necessary to ensure that the seasonality and temporal differences be balanced between the two arms. We anticipate participants will begin their treatment program (MBSR or HLC) within 8 weeks of randomization.

Severity of asthma will be classified according to criteria in the tables below. The patient's medical record will be used as the criterion reference for the medications used in classification. The list of medications will be sent to both Drs. Madison (UMMS) and Bourjeily (Miriam), the study pulmonologists, who will each make an independent determination of severity. If there is agreement between the two study pulmonologists regarding asthma severity classification, the RA will then randomize the participant according to this classification. If there is discrepancy between the two pulmonologists, the RA will provide Dr. Madison with Dr. Bourjely's assessment and rationale and Dr. Madison will make the final asthma severity classification prior to the participant being randomized.

CLASSIFICATION OF ASTHMA SEVERITY

Step 1	Step 2	Step 3	Step 4	Step 5
No controller medication. SABA as needed (Step 1 patients are not eligible for the study)	Low-dose ICS (or other low-intensity treatment such as cromolyn, LTRA, nedocromil and theophyllne)	Low-dose ICS and LABA	Med/High-dose ICS and LABA Low dose ICS+LABA+LTRA Med/High ICS/LABA +LTRA Med /high ICS/LABA +theophylline	High-dose ICS and LABA ± oral corticosteroids (and/or other extra treatment) Med/high ICS/LABA + tiotropium
Mild		**Moderate**	**Severe**	

SABA= Short-acting β_2 –agonist; ICS=inhaled corticosteroids; LABA=Long acting β_2 –agonist; LTRA=leukotriene receptor antagonists
--Steps and severity classification according to 2015 GINA guidelines (see page 21 and Box 3-5)
--Low, medium and high daily doses of inhaled corticosteroids defined per 2015 GINA guidelines (see Box 3-6)
--Alternative combinations of drugs for each step also classified per GINA 2015 guidelines
--If patient states they are on LTRA for a diagnosis other than asthma, or on oral steroids for reasons other than asthma, we will consider the medicine as an asthma therapy since it would be difficult to ascertain how they would do if that medicine was taken away.

Ms. Druker the Project Director will supervise the RAs to maintain consistent delivery of the orientation sessions, including provision of study information, obtaining informed consent, completing baseline assessments, and randomization protocol.

Retention of Participants: We expect to retain 85% of participants at 18-months. Contact information will be collected from the participant at enrollment. Tracking procedures will be established and implemented for those not completing a scheduled study assessment, or who cannot be reached. Attempts to locate participants will be made by telephone calls to family, family contacts, and directory assistance. Incentive gift certificates will be provided: $50 for completing assessments at each of the baseline and 6-month follow-ups, and $75 at 12- and 18-month follow-up. The UMMS Project Director, Ms. Susan Druker will oversee retention at both sites.

6.2.3. Blinding: All study staff except the Research Assistant, and Project Director Database Manager (Mr. William Rui) will be blinded. Blinding the Research Assistant, Project Director, and Database Manager would be impractical given that they will be randomizing the patients to the intervention groups, or tracking the randomization process. The impact of un-blinding the Research Assistant, the Project Director and the database manager will be minimal because evaluation surveys are completed directly by participants, and they will NOT perform any data entry or statistical analysis. The pulmonary lab technicians (for outcomes measurement) will be blinded, as well as the PIs, study statistician, and all study investigators and those involved with randomization codes. These un-blinded staff will have no access to the data, no influence on the outcome assessments, and no involvement in data analysis. Staff delivering the interventions and preparing reports for the independent monitoring will not be blinded.

The study arms will be coded and referred as non-informative A vs. B, but not intervention vs. control, or a coding revealing the nature of intervention arms. The non-informative coding/naming of intervention arms will be kept until the planned main outcomes analysis is completed. Unblinded project staff are prohibited to reveal the information on the coding of study arms to anyone.

The blind will be broken in the case of a serious adverse event. In this event, Drs. Madison and Bourjeily, the study pulmonary physicians, will break the blind in order to address the SAE.

The data and safety monitoring board (DSMB) will also be blinded unless the unblinding is needed to investigate severe adverse events or other patient safety issues, required by NCAAM, IRB or law.

In case the unblinding is necessary, the process will be formally monitored and documented. The PI's will draft a request for permission to unblind the codes to NCCAM, IRB and the DSMB. With the permission, the PI's will work with the database manager to reveal the study arm codes to the individuals authorized by the PI's, DSMB, NCCAM and DSMB. Hand signed documents will be kept by the database manager, and copied to DSMB, IRB and NCCAM. Unblinded individuals will be excluded from first round of statistical analysis of the main outcomes.

6.2.4 Follow-up Visits: As described in Section 6.1, study follow-up visits will occur 6- months, 12-months, and 18-months post-baseline. Section 6.2 describes the assessments that will occur at each of these time-points. Study assessment visits indicated in Section 6.2 will occur within a 3-week period before and after the 6-, 12-, and 18-month timeframes.

6.2.5 Completion/Final Evaluation: The final evaluation will be conducted at the 18-month post-baseline assessment and will consist of the assessments listed in Section 6.2 for this visit. We do not foresee any reason for participants' early termination from the study. However, any participants who discontinue study intervention early will be invited to complete all study evaluations.

7. SAFETY ASSESSMENTS

We do not foresee any risks to subjects in participating in either the MBSR or HLC interventions. MBSR is fundamentally an educational intervention and has been shown to be an effective adjunctive intervention in reducing medical symptoms for a broad range of stress-related disorders and chronic diseases, reducing psychological distress including anxiety and depression, and improving quality of life. The potential risks to participants in MSBR include psychological or social stress that might result from discussions in class. We believe that this is a minimal risk and the instructors of these classes have received excellent training on how to help individuals presenting such issues. The HLC is a series of lectures and discussions similar to those offered through the UMMHC's Community Programs office and are fundamentally educational in nature. The potential risks to participants in the HLC would be limited to psychological or social stress that may result from discussions in class. We believe this is a minimal risk and will ensure all lecturers are prepared to address

these issues should they arise.

The psychosocial assessments are standardized and widely-used paper and pencil surveys. The spirometry assessment procedures are ones asthma patients will be already familiar with from their standard medical management and do not involve risk to the patient. Likewise, the Breath Perception Discrimination Test (BPDT) that measures ability to detect small changes in resistive load will be done in the Pulmonary Diagnostic Laboratory at each site following the spirometry and does not pose any risk to participants.

A clinically significant change in spirometry reading is defined as a decrease of 15% or more from baseline to any follow-up assessment point. To monitor for untoward respiratory symptoms, the study pulmonologist, Dr. Madison, will review all participants' de-identified spirometry readings at each assessment point and compare them with their prior readings and use his clinical judgment as to whether there is any cause for concern. Should this occur, this finding will be reported to both the participating patient and the patient's pulmonologist so that they are aware of the decrease and can formulate an appropriate treatment plan.

7.1. Specification of Safety Parameters

N/A

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

N/A

7.3. Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental intervention being studied. The AE either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. An adverse finding can include a sign, symptom, abnormal assessment (e.g., laboratory test value), or any combination of these.

A **serious adverse event** (SAE) is defined as any AE 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, or an important medical event based upon appropriate medical judgment. Given the nature of the study interventions, a congenital anomaly or birth defect is a highly unlikely event and this outcome has been excluded for the present trial.

7.4 Reporting Procedures

We anticipate very minimal risk to subjects due to their participation in this study. Although our study poses minimal risk to subjects and no adverse events are expected due to the nature of the study, we will follow the adverse event procedure of the University of Massachusetts Medical School.

The University of Massachusetts Medical School/UMMC will be the coordinating institution and receive reporting of all AEs from both study sites. The current policy for reporting unanticipated problems and adverse events for the protection of human subjects in research is as follows: Any harm experienced by a subject which, in the opinion of the investigator is **unexpected** and **probably related** to the research procedures, must be reported to the IRB within 5 business days using the appropriate reporting form. A harm is **"unexpected"** when its specificity or severity are inconsistent with risk information previously reviewed and approved by the IRB in terms of nature, severity, frequency, and characteristics of the study population. A harm is **"probably related"** to the research procedures if in the opinion of the investigator, the research procedures more likely than not caused the harm. If the study is part of a multicenter trial as is this one, any AE reports received from the other sites should be sent to the UMMS IRB within 5 days of when they are received. Adverse events that do <u>not</u> meet the requirements of prompt reporting should be provided at the time continuing review is submitted. The continuing review form in the UMMS eIRB will request this information.

To assess for the occurrence of adverse events, at each assessment point participants will be asked the question: "Have there been any changes in your health since we last saw you?" We also will collect AEs that are volunteered spontaneously during interactions with participants. Any Miriam AEs will be faxed within 24 hours to the UMMS PIs. In addition, we will consider a clinically significant change in spirometry reading, defined as a decrease of 15% or more from baseline to any follow-up assessment point, as an AE. Should this occur, this finding will be reported to the patient's pulmonologist/physician so that they are aware of the decrease and allow the physician to decide if/how to follow up with the patient as appropriate.

7.5 Follow-up for Adverse Events

Should a clinically significant change in spirometry reading (defined as a decrease of 15% or more from

baseline to any follow-up assessment point) occur, this finding will be reported to both the participating patient and the patient's pulmonologist/physician so that they are aware of the decrease and can formulate an appropriate treatment plan.

All SAEs will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal); or followed until stabilization of the event has occurred (the investigators do not expect any further improvements or worsening of the event; or the event is otherwise explained regardless of whether the subject is still participating in the study. Some events do not end, such as metastasis; however, once these events are determined by the PIs to be stable or chronic, the PIs may consider the event to be resolved or resolved with sequelae.

7.6 Safety Monitoring

Monitoring will take place as per guidelines set up in collaboration with NCCAM. Initial plans for safety monitoring are as follows:

A Data and Safety Monitoring Board (DSMB) will be established. It will be made up of a pulmonologist, an expert in mindfulness research, and a biostatistician. Each has agreed to serve on the DSMB. Stephen Krinzman, M.D., is a Pulmonologist and Medical Director of the Ambulatory Clinic, Lung and Allergy Center, and the Medical Director of Allergy in the Pulmonary, Allergy and Critical Care Medicine Division of UMass Memorial Health Care. He is board certified as a Diplomate of the American Board of Internal Medicine (Pulmonary Disease, Critical Care Medicine) and a Diplomate of the American Board of Allergy and Immunology. Dr. Krinzman¹s areas of expertise are asthma management and allergic diseases. His research background includes clinical studies and basic work on the evaluation of decreased airway reactivity and inflammation with inhibition of T cell co-stimulation in a murine model of asthma. Sarah Bowen Ph.D. is Assistant Professor of Psychiatry at the University of Washington. Dr. Bowen is a clinical psychologist and has expertise and extensive experience in reviewing and analyzing data related to trials of mindfulness interventions with clinical populations. Edward Stanek III, Ph.D. is a senior biostatistician and Chair of the Department of Public Health, University of Massachusetts Amherst. Dr. Stanek has served on numerous DSMBs over the last 20 years as well as being the primary statistician of several for NHLBI-funded clinical trials and observational studies, and PI of NIH funded studies.

The board will meet annually to review data quality and safety. We also will have a core group from the research team consisting of the UMMS Principal Investigators (Drs. Lori Pbert and James Carmody), Co-Investigator (Dr. Mark Madison), Statistician (Dr. Wenjun Li) and Program Director (Susan Druker), as well as the Miriam Hospital (Dr. Ghada Bourjeily) investigator. This core group will be responsible for ongoing monitoring of the trial and reporting to our Human Subjects Committee (HSC) any issues regarding the safety of study subjects or threats to data integrity.

The Human Subjects Committee (HSC) at UMMS is a fully authorized Institutional Review Board (IRB) that provides oversight to research conducted at the medical school. It functions in compliance with the congressional statutes governing human research detailed in the University of Massachusetts Medical School "Assurance of Compliance with Health and Human Services (HHS) Regulations for Protection of Human Research Subjects". This committee will be providing oversight to the current study.

8. INTERVENTION DISCONTINUATION

MBSR has been used clinically for over two decades without any reported significant untoward effects. HLC is an educational program. We do not anticipate that any significant proportion of individuals will require discontinuation of either intervention. However, participants will be monitored at each intervention session. If individuals report moderate to severe discomfort from participation in MBSR or HLC, the participant will be extensively debriefed to ascertain the nature of the discomfort. They will be offered the choice of continuing or withdrawing from the study.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary objective of the study is to evaluate the effect of MBSR in improving asthma control. We hypothesize that asthma control as assessed by the Asthma Control Questionnaire[3] will improve significantly more in MBSR than in HLC participants at 18 month follow-up.

Secondary objectives are to evaluate whether respiratory interoceptive accuracy (Breath Perception Discrimination Test) mediates any improvements in asthma control; whether MBSR affects asthma-related QoL, lung function (change from baseline in 2-week average morning peak expiratory flow (PEF) and spirometry (Forced Expiratory Volume in 1 second (FEV_1)); and the cost-effectiveness and cost-utility of participation in MBSR on clinical outcomes.

We are employing a randomized controlled trial as the most suitable design to test the hypotheses. The measures we will use, together with their reliability and validity are described in the table of measures contained in Section 6.

9.2 Sample Size and Randomization

The trial size was determined based on hypothesized intervention effects on ACQ score, the primary outcome. We will recruit 254 individuals, but base power calculations on n=216 (108 per arm) anticipating ≦15% loss to follow-up. With one baseline measure and 3 follow-up measures at 6, 12 and 18 months, the trial can detect an intervention effect of 0.25 ACQ score improvement using ANCOVA (or linear mixed models) method at 5% significance level and at least 80% power. This treatment effect is consistent with recent reported drug-trials for asthma control. Based on literature, for sample size estimation we assumed the mean (SD) of ACQ scores for the MBSR and HLC groups are 1.24 (0.66) and 1.49 (0.66) averaged over the three follow-up time points, respectively, and a serial correlation of 0.45 within patients. We expect to recruit patients from 12 physicians at each site, with on average each physician contributing 9 patients. Because within physician correlation has not been reported in literature and our small-sized pilot study does not allow an accurate estimation, we conservatively assumed a modest within physician correlation of 0.05. The sample size was estimated using Stata MP 12.

Our sample size estimation and power analysis are conservative and the treatment effect is chosen for other important reasons: a) to preserve the possibility of addressing treatment heterogeneity by select patient and physician characteristics (e.g. differential effects between male and female participants, ethnicity); we plan to conduct subgroup analysis and examine how treatment effects may differ. Such analysis will be very important when refining the treatment protocols and for dissemination if proved effective; b) other than the primary outcome, we are also interested in other primary/secondary outcomes described below and powered the trial to detect meaningful changes in these outcomes as well. The sample size is determined to allow us to achieve all these analytic goals, not just for the primary outcome.

Randomization stratified by asthma severity and study site with each stratum in randomly allocated block sizes of two using the ralloc program in Stata[82, 83] was determined most appropriate treatment assignment procedure as it will control for the majority of confounds including disease severity, location, prior conditions, race, gender etc. Procedures for the maintenance of trial randomization codes and maintaining appropriate masking for the study have been discussed in Section 6.2.3.

In total, the study will recruit 254 participants, 127 from each of the sites. The specific recruitment goals stratified by study site and asthma severity (mild, moderate or severe asthma) are: UMass Memorial Health Care (UMMHC): and the Miriam Hospital. Data is expected on 216 participants at study completion.

9.3 Definition of Populations

We will follow the intent-to-treat principle in the primary analysis. Study arm status of patients will be coded as randomized at enrollment, and the data will also be analyzed per protocol (versus actual interventions received). We will avoid potential switch of patients between arms. We anticipate the potential switch of study arms per patient is minimal to know. For missing data (e.g., missing visits or dropouts prior study completion), we propose to use multiple imputation methods that have become the standard approach in clinical trial studies and we routinely apply using Stata MP 13 (Stata Corp., College Station, TX).

9.4 Interim Analyses and Stopping Rules

This is a fixed size RCT and no interim analysis will be conducted. Our success in meeting recruitment goals, the excellent follow-up response rate, and the effectiveness of the quality controls, and the fact that no

adverse events were reported in the pilot trial of this intervention make the necessity of stopping the present trial for these reasons a remote one.

9.5 Outcomes

9.5.1 Primary Outcome: The primary objective is to evaluate the effect of MBSR in improving asthma control as assessed by the Asthma Control Questionnaire. *Hypothesis: Asthma control as assessed by the Asthma Control Questionnaire[3] will improve significantly more in MBSR than in HLC participants at 18 month follow-up.*

9.5.2 Secondary Outcomes:

1) Asthma-related QoL. *Hypothesis: Asthma-related QoL (AQoL)[4] will improve more in MBSR than HLC participants from baseline to 18-month follow-up.*

2) Respiratory interoceptive accuracy and its mediating effect on asthma control, QoL, and medication use. *Hypotheses: MBSR will result in improved accuracy (Breath Perception Discrimination Test) at 6-, 12- and 18-months compared with HLC, and will be correlated with improved asthma control, QoL, and medication use.*

3) Lung function (change from baseline in 2-week average morning peak expiratory flow (PEF) and spirometry (Forced Expiratory Volume in 1 second (FEV_1)) at 6-, 12- and 18-months compared with HLC. *Hypotheses: There will be no deterioration, and possibly improvement, in lung function in MBSR participants from baseline to 6-, 12- and 18-months as measured by PEF and FEV_1 as compared with HLC.*

4) Cost-effectiveness in asthma control and management. Hypothesis: MBSR will be associated with improved cost-effectiveness and improved cost-utility by 18 months as compared with HLC. This will be based on clinical outcomes (e.g., asthma control, QoL, medication use) as well as quality-adjusted life years.

To conduct cost analysis, we will collect data on number of moderate and severe exacerbations, asthma-related regularly scheduled office visits, acute care visits, hospitalizations, emergency room visits, need for intubation or mechanical ventilation, and other costs during the prior 6 months at baseline, 6-, 12- and 18-month follow-up and associated clinic and hospital costs. The cost data will be determined by two methods: Self-report and actual hospital and health system costs (direct and indirect) obtained from administrative reimbursement data (see Letters of Support from fiscal offices). Brief Treatment Cost Analysis Tool (TCAT), a validated costing tool for counseling interventions,[89] will be used to calculate cost of delivering MBSR and HLC.

9.6 Data Analyses

We will follow the CONSORT Statement guideline to analyze and report the data from this trial: http://www.consort-statement.org/consort-statement/. The primary analyses will be the ITT population, that is, patient intervention status will be analyzed as randomized. As a secondary analytic goal, we will also consider per protocol analysis. Primary hypothesis*: Asthma control as assessed by the Asthma Control Questionnaire will improve more in MBSR than in HLC participants at 18-month follow-up.* We will first analyze the data descriptively by study arm (intervention vs. control) and by time point (e.g., 18 month), report descriptive statistics (mean, SD, lower and upper quartiles, median and range), and test between arm differences using t-test (normally distributed outcomes), Wilcoxon rank sum test (for skewed variables) and Chi2 test statistics (categorical variables, such as occurrence of symptoms). We will carefully examine the distributional characteristics of the outcome variables to identify proper distributional function or statistical transformations for further modeling.

Since the measures are longitudinal, we will also use linear or generalized mixed models to evaluate the intervention effects on ACQ score and presence of symptoms. We will include intervention indicator (MBSR=1 and HLC control=0) in the mixed models to estimate intervention effect. To account for auto-correlations among repeated measures on the same patient, we will include in the mixed models patient level random effects and use either first order autoregressive correlation or unstructured covariance structure for robust estimates. Within physician correlations will be modeled by including physician level random effects. We will also consider inclusion of key physician attributes such as sub-specialty in the models in order to understand how physician factors may influence the intervention effects. Since interventions will be delivered by class, we will model each class as a potential random effect in the model and test if inclusion of the class level random effect improves model estimation. If class level random effect exists, we will fit a two level hierarchical model (repeated measures on patients nested within each class). We will estimate the intervention effects with and without adjusting for patient socio-demographic and clinical co-variables. Covariate adjustments will focus co-variables that are unbalanced between the two arms, or inclusion of them will lead to substantial reduction of

variance in estimates of intervention effects, or those modifying the intervention effects. To test whether intervention effects vary by these factors, we will test the significance of the interactions between intervention indicators and each co-variable. A significant interaction term signals potential variation of intervention effect, which warrants further investigation.

To model presence of any specific component of asthma control at follow-up time points, we will use mixed effects logistic regression models. This analysis is important to understanding whether specific control component worked well or not among patients, and if there is any differential effect between the two arms. To model intervention effects on number of symptoms at each follow-up, we will use mixed effects Poisson regression models. General modeling approaches are similar to those for ACQ scores and thus not repeated, except that the underlying statistical distributions differ.

To assess the heterogeneity of intervention effects, and to identify which patient groups would benefit the most or the least from the interventions, we will conduct subgroup analysis stratified by select patient characteristics (e.g., sex, age group, severity, select symptoms, and ethnicity). We will also consider use of latent group modeling (patient profiling) to identify latent patient response groups (e.g., good responder vs. non-responder). The analysis will be conducted using Dr. Li's award-winning approach for profiling patient functional returns after total knee replacement surgeries.[100]

Secondary Outcomes: Analytic approaches for asthma-related QoL, respiratory interoceptive accuracy, lung function are generally similar to those for the two primary outcomes. To test the mediation effect of respiratory interoceptive accuracy (RIA) on asthma control, QoL, and medication use, we will first compare the difference in RIA by treatment arm. We will then use difference-to-difference approach to analyze the longitudinal associations of the changes in RIA from baseline to each follow-up time point with changes in ACQ, QoL and medication use from baseline to comparable follow-up time points.[101-103] Since we will have measures on three follow-ups, we will use linear mixed models where ACQ, QoL and medication use are treated as outcomes, RIA as the primary predictor, with and without an interaction term between RIA and MBSR indicator. These analyses will help answer whether MBSR intervention improved RIA, and whether between treatment differences in RIA would explain the observed differences in ACQ, QoL and medication use. We will compute incremental cost-effectiveness of MBSR compared with HLC as the difference in average health care costs per study participant over 18 months between MBSR and HLC, divided by the difference in average ACQ. As planned for another NIH-funded cost-effectiveness study (5R01AA009892-19), we will use the overlap between self-reported and administrative reimbursement data to estimate models of administratively estimated inpatient, outpatient, and medication services data as functions of the self-reported data. We will apply these models to all self-reported data to derive the 18-month health care costs of MBSR and HLC. We will calculate the cost of delivering the MBSR and HLC from the Brief Treatment Cost Analysis Tool (TCAT), a validated costing tool for counseling interventions.[89] Sensitivity analysis: ICER ratios will be computed between baseline and active comparator, with usual considerations of uncertainty evaluated in a probabilistic sensitivity analysis to determine the level to which our cost-effectiveness conclusions are robust.

To compare the cost-effectiveness in asthma control and management between the comparator arms we will compute per-person incremental total cost per defined measure of additional clinical benefit. More specifically, total costs will include direct and indirect costs of intervention, and per-person overall healthcare/hospital care costs over the entire follow-up period to study completion. Key clinical endpoints will include prevention of exacerbations, unscheduled acute care office visits, and emergency room visits, as well as additional quality of life achieved. We will use general linear models to analyze the associations of the person-level intervention cost with ACQ scores, and use the model to predict per-arm required intervention effects. Secondly, we will use linear models to analyze the associations of person-level intervention cost with total healthcare/hospital care cost, and examine whether increases in intervention cost are correlated with lower average healthcare/hospital care cost. This "return-on-investment" analysis will provide information on monetary savings on care cost per dollar of MBSR intervention. Following these steps, we will apply log-linear models to analyzing the intervention-to-care cost ratios, and examine whether they differ by MBSR/HLC status, and other patient/physician factors.

Missing data: For most longitudinal trial studies, missing data and dropouts are unavoidable. To account for potentially differential/informative dropouts, we will apply inverse probability weighting methods that Dr. Li developed for clinical trial studies with Dr. Pbert and associates. [104 #2421, 105] This method first estimates the probability of dropout/lost-to-follow-up of a participant based on his/her sociodemographic and health profiles, and uses the estimated probabilities as weights in the regression analysis. This method effectively removes

potential bias associated with differential lost to follow-up (e.g., unequal rate of lost to follow-up by patient attributes or by intervention conditions) while following the intent-to-treat principle. In addition, this method can be modified to hand potentially non-random missingness, such as dropouts due to poorer outcomes. For example, whether a participant drops out at time point 3 may depend on his/her outcomes at time point 2. The model can be adapted to handle outcome dependent missingness. For missing data on covariates, we propose to use multiple imputation methods that have become the standard approach in clinical trial studies and we routinely apply using Stata MP 13 (Stata Corp., College Station, TX).

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected by the study Research Assistant on both pre-tested and validated hard copy forms found to be acceptable by the type of individuals who will participate in this project and via a secure online process for patient monitoring.

We will use the Research Electronic Data Capture (RedCap) database system to manage data for this trial. REDCap originated out of the Vanderbilt Institute for Clinical and Translational Research, and has been used by numerous NIH-funded RCTs (http://www.projectredcap.org/). It has been proved to be cost-effective, efficient and robust, and very good peer-to-peer support. UMass Medical School is a member of the REDCap consortium (which has over 1,000 institutional members), and has dedicated IT staff to support the operation.

RedCap is a secure web application for building and managing online surveys and databases. Using RedCap's stream-lined process for rapidly developing projects, project staff can create and design projects using 1) the online method from your web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap. Both surveys and databases (or a mixture of the two) can be built using these methods. REDCap provides audit trails for tracking data manipulation and user activity, as well as automated export procedures for seamless data downloads to Excel, PDF, and common statistical packages (SPSS, SAS, Stata, R). Also included are a built-in project calendar, a scheduling module, ad hoc reporting tools, and advanced features, such as branching logic, file uploading, and calculated fields.

In this project, the RedCap database system will be used for both data entry/user interface and the tracking system. RedCap is fully HIPPA compliant. Regular data verification and checks for protocol compliance with data collection will occur via blinded double data entry, checks of ranges during the data entry process, and checks for values outside of allowable bounds.

Participant confidentiality will be maintained by the use of a number of strategies. Each participant will be assigned a unique study identification number. The only individual who will have access to these identifiers will be the Research Assistant responsible for data collection and Ms. Druker, the Project Director. UMMS and Miriam Hospital personnel will not be privy to identifying information about the individual participants. Subsequent protection of study data will be assured by the use of locked files and password-protected computer data bases with access available only to the principal study personnel.

10.2 Data Management:

The University of Massachusetts Medical School (UMMS), Health Statistics and Geography Lab (HSGL), will serve as the Data Management and Statistical Center. The HSGL is directed by Dr. Wenjun Li, the study biostatistician. Dr. Li will have primary responsibility for data management activities including data entry, data cleaning, and preparation of data sets. Under the direction of Dr. Li, datasets will be cleaned, verified, archived with documentation and then used to create documented SAS and STATA analysis files. All analytic and tracking database files are backed up daily. Dr. Li will oversee the data management activities with particular emphasis on ensuring the scientific integrity of all technical systems for data processing and ensuring data quality audits are done monthly.

In addition to the rigorous data entry procedure described in Section 10.1, the Project Director will monitor the quality of data collection procedures. A password protected study directory will be established on the HSGL's server for all database files and SAS analysis files. Data security will be assured through the use of limited access to the computers used for data entry and locked file drawers for data storage. In addition, only anonymous identifiers will be used in connection with data collected and stored. The key to identification of subjects will be kept in a separate and secure location.

The participating clinical sites are responsible for data collection, and securely transmit the data collection forms to the data management/statistical center for data entry and cleaning. The clinical sites are responsible for answering inquiries from the data center regarding data quality issues (such as missing items, erroneous answers). After data entry and quality control is complete, the data center is responsible for transporting the data collection forms to the project manager at UMMS to store and safe-guard the data forms in a safe location.

The data center at HSGL is responsible for producing periodic reports for monitoring the study progress, and generating data reports to be submitted to DSMB and NCCAM.

10.3 Quality Assurance

A number of procedures are in place to assure data integrity and protocol adherence. Quality control measures will include well-documented procedures, staff training and supervision, clear, pre-coded study forms and well-designed data management systems. The University of Massachusetts Medical School (UMMS), Health Statistics and Geography Lab, directed by Dr. Wenjun Li, the study biostatistician, will have primary responsibility for data management activities including data entry, data cleaning, and preparation of data sets. Data will be collected on both hard copy forms by the study Research Assistant and via a secure online process for patient monitoring. Regular data verification and checks for protocol compliance with data collection will occur via blinded double data entry, checks of ranges during the data entry process, and checks for values outside of allowable bounds. In addition to this rigorous data entry procedure, the Project Director will monitor the quality of data collection procedures. A password protected study directory will be established on the BRG's server for all database files and SAS analysis files. Data security will be assured through the use of limited access to the computers used for data entry and locked file drawers for data storage. In addition, only anonymous identifiers will be used in connection with data collected and stored. The key to identification of subjects will be kept in a separate and secure location. Under the direction of Dr. Li, the study statistician, datasets will be cleaned, verified, archived with documentation and then used to create documented SAS analysis files. All analytic and tracking database files are backed up daily. Dr. Li will oversee the data management activities with particular emphasis on ensuring the scientific integrity of all technical systems for data processing.

10.3.1. Training: The Health Educators will be trained on the HLC curriculum by Dr. Pbert, who with her colleagues developed the curriculum for a prior NCCAM-funded trial. The MBSR instructors are already trained and certified to deliver MBSR, no additional training will be required. The research staff will be trained by the Project Director on all study protocols, including recruitment, retention and data collection.

10.3.2. Quality Control Committee: A data and Safety Monitoring Board (DSMB) will be established. It will be made up of a pulmonologist, an expert in mindfulness research, and a biostatistician. Each has agreed to serve on the DSMB. Stephen Krinzman, M.D., is a Pulmonologist and Medical Director of the Ambulatory Clinic, Lung and Allergy Center, and the Medical Director of Allergy in the Pulmonary, Allergy and Critical Care Medicine Division of UMass Memorial Health Care. He is board certified as a Diplomate of the American Board of Internal Medicine (Pulmonary Disease, Critical Care Medicine) and a Diplomate of the American Board of Allergy and Immunology. Dr. Krinzman¹s areas of expertise are asthma management and allergic diseases. His research background includes clinical studies and basic work on the evaluation of decreased airway reactivity and inflammation with inhibition of T cell co-stimulation in a murine model of asthma. Sarah Bowen Ph.D. is Assistant Professor of Psychiatry at the University of Washington. Dr. Bowen is a clinical psychologist and has expertise and extensive experience in reviewing and analyzing data related to trials of mindfulness interventions with clinical populations. Edward Stanek III, Ph.D. is a senior biostatistician and Chair of the Department of Public Health, University of Massachusetts Amherst. Dr. Stanek has served on numerous DSMBs over the last 20 years as well as being the primary statistician of several for NHLBI-funded clinical trials and observational studies, and PI of NIH funded studies.

The board will meet annually to review data quality and safety. We also will have a core group from the research team consisting of the UMMS Principal Investigators (Drs. Lori Pbert and James Carmody), Co-Investigator (Dr. Mark Madison), Statistician (Dr. Wenjun Li) and Program Director (Susan Druker), as well as the Miriam Hospital investigator (Dr. Ghada Bourjeily). This core group will be responsible for ongoing monitoring of the trial and reporting to our Human Subjects Committee (HSC) any issues regarding the safety of study subjects or threats to data integrity.

The Human Subjects Committee (HSC) at UMMS is a fully authorized Institutional Review Board (IRB) that provides oversight to research conducted at the medical school. It functions in compliance with the congressional statutes governing human research detailed in the University of Massachusetts Medical School "Assurance of Compliance with Health and Human Services (HHS) Regulations for Protection of Human Research Subjects". This committee will be providing oversight to the current study.

10.3.3. Metrics: All paper-based data outcome points (primary and non-primary) and data that has been directly entered in the database will be subject to verification by a data analyst under the supervision of the study data manager. The data analyst will correct all errors during the verification process. On a monthly basis, the study data manager will perform an additional data audit of all outcome points. This audit must have an error rate less than 1%. If the error rate exceeds 1% during this secondary verification process, 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 errors encountered during the secondary audit process will be documented by the study data manager.

10.3.4. Protocol Deviations: All protocol deviations/violations and unanticipated problems will be logged on an ongoing basis throughout the study and this will be reported to the data safety monitor.

10.3.5: Monitoring: Site monitors designated by NCCAM will visit UMMS to assure protocol compliance and data quality including review of records, consents and study files. Where travel restrictions or personal distance requirements due to the COVID-19 pandemic restrict on-site visits, staff at each site will request approval from their IRB to allow remote access to NCCIH monitors to review of records, consents and study files on-line.All final protocol revisions and NCCIH PO approvals will be provided to the Miriam site in real time. Implementation will be confirmed verbally and via email by Miriam staff, and visually during UMMS site visits to Miriam via review of their records conducted every 6 months using a structured Site Visit Checklist. This Site Visit Checklist includes review of the protocol, informed consent forms, case report forms, eCRFs, source documents, participant folders, tour of the facilities, HIPPA requirements, regulations, study personnel, safety reporting, and regulatory binder.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1. Institutional Review Board (IRB) Review

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by both the UMMS IRB and the Miriam Hospital IRB. The University of Massachusetts Medical School/UMMC will be the coordinating institution, receive reporting of all AEs, and will be responsible for oversight of the study.

11.2. Informed Consent Forms

Consent will be obtained at two time points during the study: 1) at the initial phone screening, and 2) at the orientation session.

1) As in our prior studies, a HIPAA waiver authorization will be requested from our respective Institutional Review Boards prior to obtaining the list of apparently eligible patients. Interested patients will be called by the Research Assistant (RA) at each site. The RA will briefly describe the study and its requirements and it will be explained that the patient's overall care at their hospital will in no way be affected by whether or not the patient participates in the study. The RA will then enquire if the patient is still interested. If the caller is interested the RA will explain the need to collect some information from the patient to determine whether they are eligible to participate and request verbal permission to proceed. Upon obtaining verbal consent the RA will complete the phone screen which will include questions related to eligibility. A script and screening form will be used to standardize this phase of enrollment.

If the patient is eligible, the RA will schedule an in-person consent/baseline session with that individual.

2) Eligible persons will attend a consent/baseline session at the study offices at that site during which the RA will explain the study goals and procedures. This will be designed to familiarize potential participants with the study, what to expect and what is expected of their participation, both in the interventions and research assessment aspects of the study. Individuals who wish to enroll will provide written consent using an IRB-approved and dated consent 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 contact Principal Investigator. Contact information for the RA and the PI, as well as the IRB (for complaints) is provided in the consent form. Copies of the signed consent form are retained by the study and the participant. Participants are given ample opportunity to ask questions before providing consent. Ms. Druker the Project Director will supervise the RA to maintain consistent delivery of the orientation sessions. Study eligibility criteria include being aged 18 and over, and being able to read and understand English, and complete informed consent process and study data collection procedures.

After providing written consent they will complete the baseline assessments and be randomly assigned to one of the two study arms by the data manager at UMMS. Randomization will be stratified by site and asthma severity with each stratum in randomly allocated block sizes of two using the ralloc program in Stata.[82, 83] The randomizations will be conducted for each cohort to ensure that the seasonality and temporal effects be adequately controlled by design.

11.3. Participant Confidentiality

Protection of Subject Privacy: Participant confidentiality will be maintained by the use of a number of strategies. The study phone will be located in a private, locked office and be answered by the trained RA who has been trained and certified in the protection of human subjects in research trials and HIPPA requirements according to UMMS policies.

Since the interventions occur in a group setting that includes individuals not enrolled in the study it will be impossible to guarantee privacy of information that participants share in that group setting. However, at the beginning of each intervention class the instructor will emphasize the privacy of information shared in the group.

Database Protection: Data collected for eligibility screening will not contain any identifiers. These data will be entered into a secure database for later analysis of reasons for ineligibility for the study.

Each enrolled participant will be assigned a unique study identification number to maintain confidentiality. The only individual who will have access to these identifiers will be the Research Assistant responsible for data collection and Ms. Druker, the Project Director. UMMS and Miriam Hospital personnel will not be privy to identifying information about the individual participants. Subsequent protection of study data will be assured by the use of locked filing cabinets separate from the cabinets used to collect identifiers (contact information) and password-protected computer data bases with access available only to the principal study personnel. Any data, forms, reports or other records that leave the site will be identified only by the study identification number to maintain confidentiality. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NCCAM, and the OHRP. See section 10.3.2 for a description of the plan for data and safety monitoring of the research to ensure the safety of subjects.

11.4. Study Discontinuation

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

12. COMMITTEES

A steering committee consisting of UMMS Principal Investigators (Drs. Lori Pbert and James Carmody), Co-Investigator (Dr. Mark Madison), Statistician (Dr. Wenjun Li) and Program Director (Susan Druker), as well as the Miriam Hospital investigator (Dr. Ghada Bourjeily). This steering committee will be responsible for ongoing monitoring of the trial and reporting to our Human Subjects Committee (HSC) any issues regarding the safety of study subjects or threats to data integrity.

13. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Steering Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NCCAM prior to submission.

14. REFERENCES

1. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory

Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180(1):59-99.
2. Taylor DR, Bateman ED, Boulet LP, et al. A new perspective on concepts of asthma severity and control. Eur Respir J. 2008;32(3):545-54.
3. Juniper EF, O'Byrne PM, Ferrie PJ, King DR, Roberts JN. Measuring asthma control. Clinic questionnaire or daily diary? Am J Respir Crit Care Med. 2000;162(4 Pt 1):1330-4.
4. Juniper EF, Guyatt GH, Ferrie PJ, Griffith LE. Measuring quality of life in asthma. Am Rev Respir Dis. 1993;147(4):832-8.
5. U.S. Department of Health and Human Services. Vital and Health Statistics. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2008. Hyattsville, Maryland: National Center for Health Statistics, 2009 Contract No.: Serios 10, Number 242.
6. Asthma and Allergy Foundation of America. The costs of asthma. Asthma and Allergy Foundation 1992 and 1998 study, 2000 update. www.aafa.org2000.
7. Juniper EF. The impact of patient compliance on effective asthma management. Curr Opin Pulm Med. 2003;9 Suppl 1:S8-10.
8. Siroux V, Boudier A, Anto JM, et al. Quality-of-life and asthma-severity in general population asthmatics: results of the ECRHS II study. Allergy. 2008;63(5):547-54.
9. Strine TW, Ford ES, Balluz L, Chapman DP, Mokdad AH. Risk behaviors and health-related quality of life among adults with asthma: the role of mental health status. Chest. 2004;126(6):1849-54.
10. Wong KO, Hunter Rowe B, Douwes J, Senthilselvan A. Asthma and wheezing are associated with depression and anxiety in adults: an analysis from 54 countries. Pulmonary Medicine. 2013;2013:929028.
11. Cooper CL, Parry GD, Saul C, et al. Anxiety and panic fear in adults with asthma: prevalence in primary care. BMC family practice. 2007;8:62.
12. Lehrer P, Feldman J, Giardino N, Song HS, Schmaling K. Psychological aspects of asthma. J Consult Clin Psychol. 2002;70(3):691-711.
13. Rietveld S, van Beest I. Rollercoaster asthma: when positive emotional stress interferes with dyspnea perception. Behav Res Ther. 2006;45(5):977-87.
14. Janssens T, Verleden G, De Peuter S, Van Diest I, Van den Bergh O. Inaccurate perception of asthma symptoms: a cognitive-affective framework and implications for asthma treatment. Clin Psychol Rev. 2009;29(4):317-27.
15. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. JAMA. 2002;287(5):622-7..
16. Rietveld S, Prins PJM, Colland VT. Accuracy of symptom perception in asthma and illness severity. Children's Health Care. 2001;30(1):27-41.
17. Janson C, Bjornsson E, Hetta J, Boman G. Anxiety and depression in relation to respiratory symptoms and asthma. Am J Respir Crit Care Med. 1994;149(4 Pt 1):930-4.
18. Rimington LD, Davies DH, Lowe D, Pearson MG. Relationship between anxiety, depression, and morbidity in adult asthma patients. Thorax. 2001;56(4):266-71.
19. Kolbe J, Vamos M, Fergusson W, Elkind G. Determinants of management errors in acute severe asthma. Thorax. 1998;53(1):14-20.
20. Yii AC, Koh MS. A review of psychological dysfunction in asthma: affective, behavioral and cognitive factors. J Asthma. 2013 Jul 29.
21. Strine TW, Mokdad AH, Balluz LS, Berry JT, Gonzalez O. Impact of depression and anxiety on quality of life, health behaviors, and asthma control among adults in the United States with asthma, 2006. J Asthma. 2008;45(2):123-33.
22. Adams RJ, Wilson DH, Taylor AW, et al. Psychological factors and asthma quality of life: a population based study. Thorax. 2004;59(11):930-5.
23. Smith A, Nicholson K. Psychosocial factors, respiratory viruses and exacerbation of asthma. Psychoneuroendocrinology. 2001;26(4):411-20.
24. ten Thoren C, Petermann F. Reviewing asthma and anxiety. Respir Med. 2000;94(5):409-15.
25. Magid DJ, Houry D, Ellis J, Lyons E, Rumsfeld JS. Health-related quality of life predicts emergency department utilization for patients with asthma. Ann Emerg Med. 2004;43(5):551-7.
26. Archea C, Yen IH, Chen H, et al. Negative life events and quality of life in adults with asthma. Thorax.

2007;62(2):139-46.
27. Dennis SM, Edwards S, Partridge MR, Pinnock HJ, Qureshi SJ. The dissemination of the British Guideline on the Management of Asthma 2003. Respir Med. 2004;98(9):832-7.
28. Institute of Medicine. Crossing the quality chasm: A new health system for the 21st century. 2001.
29. Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. Respir Med. 2009;103(5):670-91.
30. Clark N, Lachance L, Milanovich AF, Stoll S, Awad DF. Characteristics of successful asthma programs. Public Health Rep. 2009;124(6):797-805.
31. Yorke J, Fleming SL, Shuldham C. Psychological interventions for adults with asthma: a systematic review. Respir Med. 2007;101(1):1-14.
32. Gyorik SA, Brutsche MH. Complementary and alternative medicine for bronchial asthma: is there new evidence? Curr Opin Pulm Med. 2004;10(1):37-43.
33. Ritz T, Dahme B, Roth WT. Behavioral interventions in asthma; Biofeedback techniques. J Psychosom Res. 2004;56(6):711-20.
34. Lehrer PM, Vaschillo E, Vaschillo B, et al. Biofeedback treatment for asthma. Chest. 2004;126(2):352-61.
35. Ritz T. Relaxation therapy in adult asthma. Is there new evidence for its effectiveness? Behav Modif. 2001;25(4):640-66.
36. Markham AW, Wilkinson JM. Complementary and alternative medicines (CAM) in the management of asthma: an examination of the evidence. J Asthma. 2004;41(2):131-9.
37. Steurer-Stey C, Russi EW, Steurer J. Complementary and alternative medicine in asthma: do they work? Swiss Med Wkly. 2002;132(25-26):338-44.
38. Huntley A, White AR, Ernst E. Relaxation therapies for asthma: a systematic review. Thorax. 2002;57(2):127-31.
39. Deshmukh VM, Toelle BG, Usherwood T, O'Grady B, Jenkins CR. Anxiety, panic and adult asthma: a cognitive-behavioral perspective. Respir Med. 2007;101(2):194-202.
40. Bogaerts K, Notebaert K, Van Diest I, Devriese S, De Peuter S, Van den Bergh O. Accuracy of respiratory symptom perception in different affective contexts. J Psychosom Res. 2005;58(6):537-43.
41. Carmody J. Evolving conceptions of mindfulness in clinical settings. Journal of Cognitive Psychotherapy. 2009;23(3):270-80.
42. Miller JJ, Fletcher K, Kabat-Zinn J. Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. Gen Hosp Psychiatry. 1995;17(3):192-200.
43. Baer RA. Mindfulness Training as a Clinical Intervention: A Conceptual and Empirical Review. Clin Psychol. 2003;10(2):125-43.
44. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits; A meta-analysis. J Psychosom Res. 2004;57(1):35-43.
45. Modinos G, Ormel J, Aleman A. Individual differences in dispositional mindfulness and brain activity involved in reappraisal of emotion. Social cognitive and affective neuroscience. 2010;5(4):369-77.
46. Williams JM. Mindfulness and psychological process. Emotion. 2010;10(1):1-7.
47. Teasdale JD. Metacognition, mindfulness and the modification of mood disorders. Clinical Psychology and Psychotherapy. 1999;6:146-55.
48. Teasdale JD, Segal ZV, Williams JMG, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. Journal of Consulting & Clinical Psychology. 2000;68(4):615-23.
49. Hargus E, Crane C, Barnhofer T, Williams JM. Effects of mindfulness on meta-awareness and specificity of describing prodromal symptoms in suicidal depression. Emotion. 2010;10(1):34-42.
50. Ryan RM, Kuhl J, Deci EL. Nature and autonomy: an organizational view of social and neurobiological aspects of self-regulation in behavior and development. Dev Psychopathol. 1997;9(4):701-28.
51. Fjorback LO, Arendt M, Ornbol E, Fink P, Walach H. Mindfulness-based stress reduction and mindfulness-based cognitive therapy: a systematic review of randomized controlled trials. Acta Psychiatr Scand. 2011;124(2):102-19.
52. Anderson ND, Lau MA, Segal ZV, Bishop SR. Mindfulness-based stress reduction and attentional control. Clinical Psychology and Psychotherapy. 2007;14(6):449-63.

53. Jha AP, Krompinger J, Baime MJ. Mindfulness training modifies subsystems of attention. Cognitive, affective & behavioral neuroscience. 2007;7(2):109-19.
54. MacLean KA, Ferrer E, Aichele SR, et al. Intensive meditation training improves perceptual discrimination and sustained attention. Psychol Sci. 2010;21(6):829-39.
55. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: A meta-analytic review. J Consult Clin Psychol. 2010;78(2):169-83.
56. Carmody J, Baer RA, E LBL, Olendzki N. An empirical study of the mechanisms of mindfulness in a mindfulness-based stress reduction program. J Clin Psychol. 2009;65(6):613-26.
57. Jain S, Shapiro SL, Swanick S, et al. A randomized controlled trial of mindfulness meditation versus relaxation training: effects on distress, positive states of mind, rumination, and distraction. Ann Behav Med. 2007;33(1):11-21.
58. Epel E, Daubenmier J, Moskowitz JT, Folkman S, Blackburn E. Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres. Ann N Y Acad Sci. 2009;1172:34-53.
59. Daubenmier J, Sze J, Kerr CE, Kemeny ME, Mehling W. Follow your breath: respiratory interoceptive accuracy in experienced meditators. Psychophysiology. 2013;50(8):777-89.
60. Mirams L, Poliakoff E, Brown RJ, Lloyd DM. Brief body-scan meditation practice improves somatosensory perceptual decision making. Conscious Cogn. 2012;22(1):348-59.
61. Rietveld S. Symptom perception in asthma: a multidisciplinary review. J Asthma. 1998;35(2):137-46.
62. Carmody J, Baer RA. Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. J Behav Med. 2008;31(1):23-33.
63. Nyklicek I, Kuijpers KF. Effects of mindfulness-based stress reduction intervention on psychological well-being and quality of life: is increased mindfulness indeed the mechanism? Ann Behav Med. 2008;35(3):331-40.
64. Orzech KM, Shaprio SL, Brown KW, McKay M. Intensive mindfulness training-related changes in cognitive and emotional experience. The Journal of Positive Psychology. 2009;4(3):212-22.
65. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. Psychoneuroendocrinology. 2004;29(4):448-74.
66. Carlson LE, Garland SN. Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. Int J Behav Med. 2005;12(4):278-85.
67. Britton WB, Bootzin RR, Cousins JC, Hasler BP, Peck T, Shapiro SL. The contribution of mindfulness practice to a multicomponent behavioral sleep intervention following substance abuse treatment in adolescents: a treatment-development study. Substance abuse: Official publication of the Association for Medical Education and Research in Substance Abuse. 2010;31(2):86-97.
68. Tacon AM, McComb K, Caldera Y, Randolph P. Mindfulness meditation, anxiety reduction, and heart disease: a pilot study. Family & Community Health. 2003;26(1):25-33.
69. Lazarus R, Folkman S. Stress, Appraisal, and Coping. New York, NY: Springer Publishing Company; 1984.
70. Pbert L, Madison JM, Druker S, et al. Effect of mindfulness training on asthma quality of life and lung function: a randomised controlled trial. Thorax. 2012;67(9):769-76.
71. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994;47(1):81-7.
72. Pearlman DS, Berger WE, Kerwin E, Laforce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. J Allergy Clin Immunol. 2005;116(6):1206-12.
73. Boulet LP, Bateman ED, Voves R, Muller T, Wolf S, Engelstatter R. A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. Respir Med. 2007;101(8):1677-86.
74. Israel E, Cohn J, Dube L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. JAMA. 1996;275(12):931-6.
75. Holgate ST, Chuchalin AG, Hebert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. Clin Exp Allergy. 2004;34(4):632-8.

76. National Heart Lung and Blood Institute (NHLBI). Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. NIH Publication NO. 07-4051. U.S. Department of Health and Human Services, http://www.nhibi.nih.gov/guidelines/asthma/asthgdin.htm, 2007.
77. National Heart L, and Blood Institute. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Bethesda 2007 Contract No.: Publication no. 97-4051.
78. Kullowatz A, Rosenfield D, Dahme B, Magnussen H, Kanniess F, Ritz T. Stress effects on lung function in asthma are mediated by changes in airway inflammation. Psychosom Med. 2008;70(4):468-75.
79. Mrazek DA. Psychiatric symptoms in patients with asthma causality, comorbidity, or shared genetic etiology. Child Adolesc Psychiatr Clin N Am. 2003;12(3):459-71.
80. Cohen J. Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
81. Crawford JR, Henry JD, Crombie C, Taylor EP. Normative data for the HADS from a large non-clinical sample. Br J Clin Psychol. 2001;40(4):429-34.
82. Ryan P. Update to random allocation of treatment to blocks. Stata Technical Bulletin. 1999;50:36-7.
83. Ryan P. Random allocation of treatments in blocks. Stata Technical Bulletin. 1998;41:43-6.
84. Kabat-Zinn J. Full catastrophe living: using the wisdom of your body and mind to face stress, pain and illness. New York: Delacorte; 1990.
85. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005;99(5):553-8.
86. Wells KE, Peterson EL, Ahmedani BK, Williams LK. Real-world effects of once vs greater daily inhaled corticosteroid dosing on medication adherence. Ann Allergy Asthma Immunol. 2013;111(3):216-20.
87. Fresco DM, Moore MT, van Dulmen MH, et al. Initial psychometric properties of the experiences questionnaire: validation of a self-report measure of decentering. Behav Ther. 2007;38(3):234-46.
88. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest. 1999;115(5):1265-70.
89. Shepard DS, Zeng W, Strickler GK, Lwin AK, Cros MJ, Garner BR. The Brief Treatment Cost Analysis Tool (TCAT-Lite) for Substance Abuse Treatment: Reliability and Application. Alcoholism treatment quarterly. 2012;30(4):377-96.
90. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med. 1995;152(3):1107-36.
91. Baer RA, Smith GT, Hopkins J, Krietemeyer J, Toney L. Using self-report assessment methods to explore facets of mindfulness. Assessment. 2006;13(1):27-45.
92. Baer RA, Carmody J, Hunsinger M. Weekly change in mindfulness and perceived stress in a mindfulness-based stress reduction program. J Clin Psychol. 2012;68(7):755-65.
93. Baer RA, Smith GT, Lykins E, et al. Construct validity of the five facet mindfulness questionnaire in meditating and nonmeditating samples. Assessment. 2008;15(3):329-42.
94. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
95. Linville PW. Self-complexity as a cognitive buffer against stress-related illness and depression. J Pers Soc Psychol. 1987;52(4):663-76.
96. Glasgow RE, Klesges RC, Mizes JS, Pechacek TF. Quitting smoking: strategies used and variables associated with success in a stop-smoking contest. J Consult Clin Psychol. 1985;53(6):905-12.
97. Frenzel MP. The relationship of stress and coping to regimen adherence and glycemic control of diabetes. Journal of Social and Clinical Psychology. 1988;6(1):77-87.
98. Carmody J, Reed G, Kristeller J, Merriam P. Mindfulness, spirituality, and health-related symptoms. J Psychosom Res. 2008;64(4):393-403.
99. Aalto AM, Harkapaa K, Aro AR, Rissanen P. Ways of coping with asthma in everyday life: validation of the Asthma Specific Coping Scale. J Psychosom Res. 2002;53(6):1061-9.
100. Franklin PD, Li W, Ayers DC. The Chitranjan Ranawat Award: functional outcome after total knee replacement varies with patient attributes. Clin Orthop Relat Res. 2008;466(11):2597-604.
101. Blundell R, Dias M. Alternative approaches to evaluation in empirical microeconomics. J Hum Resour. 2009;44(3):565-640.
102. Meyer BD, Viscusi WK, Durbin DL. Workers' compensation and injury duration: evidence from a natural

experiment. The American economic review. 1995;85(3):322-40.
103. Villa J. DIFF: Stata Module to Perform Differences in Differences Estimation. Statistical Software Components. Boston College Department of Economics2011.
104. Lemon SC, Wang ML, Wedick NM, et al. Weight gain prevention in the school worksite setting: results of a multi-level cluster randomized trial. Prev Med. 2014;60:41-7.
105. Lemon SC, Zapka J, Li W, et al. Step ahead a worksite obesity prevention trial among hospital employees. Am J Prev Med. 2010;38(1):27-38.