STUDY PROTOCOL

MAP
Mind-Body Approaches to Pain

Comparison of CAM and Conventional Mind-Body Therapies for Chronic Back Pain

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PROTOCOL HIGHLIGHTS

TITLE	**Mind-Body Approaches to Pain (MAP Study)**
INVESTIGATORS	Dan Cherkin, PhD, Principal Investigator Group Health Research Institute, Seattle Karen Sherman, Ph.D., MPH, Co-Investigator Group Health Research Institute, Seattle Andrea Cook, Ph.D., Co-Investigator Group Health Research Institute, Seattle Ben Balderson, Ph.D., Co-Investigator Group Health Research Institute, Seattle Judith Turner, PhD, Co-Investigator University of Washington, Seattle
POPULATION/SITE	Members of Group Health Cooperative (Seattle) health plan who are 20 through 64 years of age, have had at least 3 months of continuous non-specific low back pain, and who rate the bothersomeness of their pain at least 4 on a 0 to 10 scale and have a score of at least 3 on a 0 to 10 Pain Interference Scale.
INTERVENTIONS	Participants will be randomized to one of three treatments: • Cognitive Behavioral Therapy (CBT) • Mindfulness-Based Stress Reduction (MBSR) • Usual medical care
INTERVENTION SCHEDULE	8 weekly classes of CBT or MBSR plus daily home practice
SAMPLE SIZE	297 participants (99 CBT, 99 MBSR, 99 usual care)
RECRUITMENT PERIOD	Participants will be recruited in 9 cohorts of 33 persons each over a 24-month recruitment period
STUDY AIMS	1) To determine whether Mindfulness-Based Stress Reduction (MBSR) is an effective adjunct to usual medical care for persons with chronic back pain.

	2) To compare the effectiveness of MBSR and group Cognitive-Behavioral Therapy (CBT) in decreasing back pain-related functional limitations and pain bothersomeness. 3) To identify the mediators of any observed effects of MBSR and group CBT on pain-related functional limitations and pain bothersomeness. 4) To compare the cost-effectiveness of MBSR and group CBT as adjuncts to usual care for persons with chronic back pain.
Co-PRIMARY TRIAL OUTCOMES	1) Modified Roland-Morris Disability Questionnaire (back-related dysfunction). This is the most important outcome and was used to calculate statistical power for Aims 1and 2. 2) Bothersomeness of low back pain (0 to 10 scale). These outcomes will be measured at baseline, at 4 weeks (during classes), 8 weeks (at the end of classes), 26, and 52 weeks. The 26 week outcomes will be used as the primary endpoint and all other time-points will be considered secondary evaluations.
SAFETY OUTCOMES	Any adverse events identified during classes, on the follow-up interviews or through other means will be documented and reported on a regular basis to the Data Safety Monitoring Body (DSMB). Serious adverse experiences will be reported to the DSMB within 7 days. If attributable to the interventions, serious adverse experiences will also be reported to the IRB within 7 days.
POTENTIAL MEDIATING VARIABLES	We hypothesize: 1) that any benefits of MBSR on participant function and pain bothersomeness will be mediated through increased participant mindfulness and acceptance of pain, and 2) that any benefits of CBT will be mediated through changes in specific cognitions and coping behaviors, as listed in the Specific Aims. We will assess each potential mediator in each follow-up interview.

Mediators of MBSR Effects on Outcomes:
Mindfulness will be assessed using the validated short form version of the 5-Facet Mindfulness Questionnaire.
Acceptance of pain will be measured with the Chronic Pain Acceptance Questionnaire (CPAQ), a valid and reliable instrument which measures: 1) activities engagement (pursuit of life activities even while pain is experienced) and, 2) "pain willingness" (recognition that strategies for avoiding or controlling pain are ineffective).

Mediators of CBT Effects on Outcomes:

Pain Beliefs will be measured using three scales from the Survey of Pain Attitudes scale (SOPA): *Disability* (belief that one's pain is disabling), *Harm* (belief that pain signifies damage and that activity should be avoided), and *Control* (belief in one's control over pain). These scales have good test-retest stability, validity, and internal consistency.

Catastrophizing will be measured with the Pain Catastrophizing Scale (PCS), which has demonstrated reliability and validity, and test-retest stability.

Self-efficacy for managing chronic pain will be assessed with the 10-item Patient Self-Efficacy Questionnaire (PSEQ), which has been found to be valid and reliable.

Pain Coping will be measured using 4 scales from the Chronic Pain Coping Inventory (CPCI), which assesses strategies used to cope with chronic pain. The Relaxation, Task Persistence, Coping Self-statements, and Rest scales will be used because they address coping strategies targeted by CBT interventions. These scales have demonstrated internal consistency, test-retest reliability, and validity.

MASKING	All persons collecting outcome information (i.e., interviewers) will be masked to each participant's group assignment.

ANALYSIS	Individuals will be analyzed by randomized group regardless of treatments received (i.e., an intention to treat analysis will be used). Analyses will utilize generalized estimating equations (GEE) to account for repeated measures on a given individual (i.e. 4, 8, 26, and 52 week measurements) for both co-primary outcomes. However, since the 26-week time point is the primary time point the treatment can only be deemed successful if the 26-week time point is successful. The other time points are considered secondary evaluations. The mean model will include an interaction between time of measurement and treatment groups (ANCOVA model) and adjustment for potential confounders and baseline outcome measurements. Omnibus tests of differences between treatment groups at each time measurement will be assessed within this GEE model framework. If the overall treatment effect is significant at a given time point then pairwise comparisons between treatment groups will be performed.
CLINICAL SIGNIFICANCE	Mean treatment effect differences exceeding 2.5 points on the Roland scale and 1.5 points on the bothersomeness scale will be considered clinically significant.

STATISTICAL POWER

When analyzing the co-primary outcomes as continuous measures, we will have 90% power to detect a 2.95 point difference in the modified Roland Score and a 1.78 point difference in Bothersomeness score. Thus, we will have ample power for detecting clinically meaningful differences since differences of 2.5 on the Roland scale and 1.5 on the bothersomeness scale are considered clinically meaningful. Assuming 11% loss to follow-up (slightly higher than was found in our previous back pain trials), we plan to recruit a total sample size of 297 participants (99 per group).

Both co-primary outcomes will be tested at the $p < 0.05$ level at each time point because they address separate scientific questions. Analyses of both co-primary outcomes at all follow-up times will be reported, imposing a more stringent requirement than simply reporting a sole significant outcome.

1. INTRODUCTION

Identifying cost-effective treatments for chronic low back pain (CLBP) remains a huge challenge for clinicians, researchers, payers, and patients. About $26 billion is spent annually in the U.S. in direct costs of medical care for back pain, and in 2002, the estimated costs of lost worker productivity due to back pain were $19.8 billion. Despite the vast number of options for evaluating and treating back pain, and the greatly increased medical care resources devoted to this problem, the health and functional status of persons suffering from back pain in the U.S. has deteriorated. Furthermore, both providers and patients are dissatisfied with the status quo and millions of persons with back pain have yet to find adequate relief.

In recent years, there has been an increasing appreciation that patient psychological factors, such as pain-related beliefs, thoughts, and coping behaviors, can have a significant impact on the experience of pain and its effects on various aspects of functioning. Therefore, there is a clear rationale for chronic pain therapies, such as cognitive-behavioral therapies (CBT) and mindfulness-based stress reduction (MBSR), which target psychosocial variables. Indeed, cognitive-behavioral therapies have been demonstrated effective for a variety of chronic pain problems, including back pain. In fact, 4 of the 8 nonpharmacologic treatments recommended by the ACP/APS guidelines for persistent back pain (yoga, CBT, intensive interdisciplinary rehabilitation, and progressive relaxation) include such “mind-body” components.

In view of the large personal and societal impact of chronic back pain; the, at best, moderate effectiveness of current treatments; the promising results of the few trials that have evaluated mind-body therapies; and the popularity, safety, and fairly low cost of mind-body therapies, further research on the comparative effectiveness and cost-effectiveness of mind-body therapies should be a priority for back pain research. Many existing treatments are not only lacking in evidence, but also carry substantial risks and costs. Furthermore, many individuals lack access (due to where they live and/or insurance coverage) to treatments that are effective (e.g., psychologists trained in CBT for chronic pain). Therefore, we will conduct a randomized trial to evaluate the effectiveness and cost-effectiveness for chronic back pain of MBSR, and to compare it to group CBT, an established mind-body therapy of proven effectiveness. Because MBSR includes 3 popular CAM mind-body therapies (breathing, yoga, meditation), both additive and synergistic effects among its components may contribute to its effectiveness for chronic back pain.

We believe that the proposed trial is significant because it:

1. Evaluates the effectiveness and cost-effectiveness of a promising CAM mind-body therapy (MBSR) for chronic back pain, a common, costly, and debilitating public health problem lacking safe and highly effective treatment options.
2. Compares the effectiveness and cost-effectiveness of MBSR with CBT, a treatment of proven effectiveness but limited availability because it is typically delivered by PhD-level clinical psychologists with expertise in chronic pain. Unlike CAM therapies such as chiropractic and massage, MBSR is a self-care tool that, once learned, can be used any time, anywhere, and without cost. Thus, if MBSR is found cost-effective, it would expand the relatively small number of good treatment options available to Americans suffering from chronic back pain.

3. Includes mediator analyses to increase understanding of the mechanisms through which mind-body therapies reduce pain and improve patient functioning. Such knowledge has value for refining theoretical models of chronic pain and for developing more powerful and efficient therapies.

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2. PROJECT OVERVIEW

We propose a randomized trial to evaluate the effectiveness and cost-effectiveness of Mindfulness-Based Stress Reduction (MBSR) for treating chronic back pain, and to compare it to group CBT, a conventional mind-body therapy. MBSR includes meditative practices, mindful yoga, and group discussions aimed at enhancing awareness in daily life. It incorporates 3 of the most popular CAM mind-body techniques. MBSR has been used by more than 18,000 Americans for back pain and other chronic conditions. Our specific aims are:

Aim 1. To determine whether Mindfulness-Based Stress Reduction (MBSR) is an effective adjunct to usual medical care for persons with chronic back pain.
Hypothesis 1: Patients randomized to an MBSR course will show greater short-term (8 and 26 weeks) and long-term (52 weeks) improvement in pain-related functional limitations, pain bothersomeness, and other health outcomes as compared with those randomized to continued usual care alone.

Aim 2. To compare the effectiveness of MBSR and group Cognitive-Behavioral Therapy (CBT) in decreasing back pain-related functional limitations and pain bothersomeness.
Hypothesis 2: MBSR will be more effective than group CBT in decreasing pain-related functional limitations and pain bothersomeness in both the short and long term. The rationale for this hypothesis is based on: a) the modest effectiveness of CBT for chronic back pain found in past studies, b) the positive results of the limited initial research evaluating MBSR for chronic back pain, and c) growing evidence that an integral part of MBSR (but not CBT) training, yoga, is effective for chronic back pain.

Aim 3. To identify the mediators of any observed effects of MBSR and group CBT on pain-related functional limitations and pain bothersomeness.
Hypothesis 3a: The effects of MBSR on functional limitations and pain will be mediated by increases in mindfulness and acceptance of pain.
Hypothesis 3b: The effects of CBT on functional limitations and pain will be mediated by changes in pain-related cognitions (decreases in catastrophizing and beliefs one is disabled by pain and that pain signals harm, increases in perceived control over pain and self-efficacy for managing pain) and coping behaviors (increased use of relaxation, task persistence, and coping self-statements; decreased use of rest).

Aim 4. To compare the cost-effectiveness of MBSR and group CBT as adjuncts to usual care for persons with chronic back pain.
Hypothesis 4: Both MBSR and group CBT will be cost-effective adjuncts to usual care.

We will also explore whether certain patient characteristics predict or moderate treatment effects. For example, we will explore whether patients with higher levels of depression are less likely to improve with both treatments (i.e., depression level is a nonspecific predictor of treatment effects), or whether such patients are more likely to benefit from CBT than from MBSR (i.e., depression level is a moderator of treatment effects).

If MBSR and/or group CBT are more effective than usual care alone, and found to be cost-effective, this evidence could help inform policy decisions for chronic back pain care. Because of the high prevalence and costs of this problem, safe and low cost treatments of even modest effectiveness could produce a large benefit on a population level**.** Knowledge gained concerning therapeutic mechanisms and patient subgroups most likely to benefit from each of these treatments could help target specific treatments to those most likely to benefit, as well as help refine treatments to be more powerful and efficient.

3. TRIAL DESIGN

3.1 Overall Design

To determine whether CBT and MBSR are more effective treatments for persons with chronic back pain than usual care we will conduct a randomized trial comparing CBT and MBSR interventions with usual care.

We will recruit health plan patients from 20 to 64 years of age whose back pain persists at least 3 months after a primary care visit with a diagnosis indicating non-specific low back pain. Eligible and willing participants will be randomized to one of three groups in a 1:1:1 ratio: CBT, MBSR or usual care. The CBT and MBSR class series will consist of 8 weekly 2 hour sessions supplemented by daily practice at home.

Participants will be followed for 52 weeks after randomization. Interviewers masked to participants' treatment assignments will assess outcomes after 4, 8, 26, and 52 weeks post randomization. The primary outcomes will be pain-related functional limitations and symptom bothersomeness. Bias will be minimized by a rigorous randomization procedure, by describing the study as one of two different "mind-body approaches" to treating back pain, and by having interviewers masked to the participant's treatment group.

3.2. Study Population

Participants will be recruited from Group Health Cooperative, a group-model, not-for-profit health care organization that serves over 400,000 enrollees through its own primary care facilities in Western Washington. GHC members with chronic low back pain of mechanical origin (as opposed to infectious, neoplastic, or inflammatory causes) will be eligible to participate.

3.3 Inclusion and Exclusion Criteria

Health plan members from 20 through 64 years of age with a ICD-9 diagnoses indicative of non-specific low back pain and whose pain has persisted at least three months will be eligible for the study if they rate their low back pain at least 4 on a 0 to 10 back pain bothersomeness scale, their activity limitations at least 3 on a 0 to 10 pain interference scale, and give informed consent. Uncomplicated mechanical back pain

was chosen as the condition for study because it is a common and expensive problem and a leading reason that people seek care from CAM providers. Inclusion and exclusion criteria were developed to maximize the enrollment of appropriate patients while screening out patients who: have low back pain of a specific (e.g., spinal stenosis) or complicated (e.g., due to a medical condition) nature, or for whom CBT or MBSR is contraindicated (i.e., psychosis). These criteria are intended to exclude patients with medical conditions that: might contribute to an increased risk of an adverse event, would not allow for fully informed consent, or might lead to misinterpretation of the data (e.g., multiple sclerosis or diabetes with neurological symptoms that might interfere with pain sensation). Reasons for exclusion will be identified from two sources: 1) automated data on ICD-9 diagnoses recorded during all visits over the previous year made by health plan members identified with low back pain-compatible ICD-9 diagnoses, 2) telephone eligibility interviews. The following table lists the inclusion and exclusion criteria, the rationale for each criterion, and the source of information:

INCLUSION CRITERIA	**Rationale**	**Source***
Continuing member of Group Health Cooperative	Defined population that is easy to identify, recruit and follow-up	A, TI
20 through 64 years of age	Chronic low back pain in children results from different causes than those we are studying; older persons have higher risk of undiagnosed serious conditions causing low back pain	A
At least one primary care visit for back pain within the past 3-15 months	Efficient method for identifying people who may have chronic low back pain and who have been evaluated by a physician for their problem	A
Non-specific, uncomplicated low back pain, i.e., these ICD-9 codes: 724.2 Lumbago 724.5 Backache, unspecified 724.8 Other symptoms referable to back 846.0-9 Sprains and strains, sacroiliac 847.2 Sprains and strains, lumbar 847.3 Sprains and strains, sacral 847.9 Sprains and strains, unspecified site of the back	These codes are consistent with low back pain that is uncomplicated and mechanical in nature	A

*A = Automated visit data

EXCLUSION CRITERIA	**Rationale**	**Source***
Low back pain has lasted < 3 months	Low back pain not chronic	TI
Bothersomeness of pain score of < 4 and Pain Interference Score of <3.	Back pain too mild to be able to detect improvement	TI
Abdominal Aneurism	Back pain due to, or possibly result of, specific disease/condition	A
Cancer, metastatic		A, TI
Discitis		A
Disk disease		A
Fracture of vertebra		A, TI
Infectious cause of back pain		TI
Pregnancy		TI
Scoliosis, severe or progressive		A, TI
Spinal stenosis		A, TI
Spondylolisthesis		A, TI
Sciatica	Back problem of complicated nature, including medico-legal issues	TI
Seeking/receiving compensation/litigation for back pain		TI
Surgery, previous back, ever		TI
Blindness	Condition might make it difficult to attend the classes or practice at home	A
Deafness		A
No way to play audio home practice recordings at home		TI
Paralysis		A
Psychoses, major		A, TI
Schedules do not permit participation in classes or home practice (including planning to move out of town)		TI
Vision problems, severe		TI
Hearing problems, severe		TI

Lack of transportation		TI
Fibromyalgia Rheumatoid arthritis/Anklyosing spondylitis Other disabling chronic conditions (e.g., disabling heart or lung disease, diabetic neuropathy, receiving treatment for hepatitis) Planning on seeing a specialist for low back pain such as a surgeon, neurologist, or rheumatologist	Condition/circumstance might confound treatment effects or interpretation of data	TI A, TI TI TI
Dementia Unable to read or speak English	Condition would make it difficult for fully-informed consent	A TI
Currently taking a mind-body class for back pain or has used one in past year	Possible bias due to current or recent intervention users	TI

*A = Automated visit data
*TI = Telephone interview

Members determined to have any of the following during the telephone eligibility screening interview will be excluded: non-mechanical causes or potential causes of low back pain (i.e., sciatica, underlying systemic or visceral disease, pregnancy, spondylolisthesis, spinal stenosis, cancer or unexplained weight loss, recent vertebral fracture); current use of a mind-body therapy for their back pain; characteristics complicating the interpretation of findings (i.e., involved with litigation or compensation claim for back pain, evidence of severe or progressive neurologic deficits, previous back surgery, regardless of time since performed, planning to see a specialist for low back pain (i.e., surgeon, neurologist, rheumatologist), unstable medical or severe psychiatric conditions; characteristics related to ability to complete the study protocol (i.e., unable to speak or read English, plan to move out of town). In addition, we will require that participants be willing and able to attend the CBT or MBSR classes during the 8-week intervention period and to respond to the 4 follow-up questionnaires assessing outcomes.

3.4 Recruitment Procedures:

Because the study intervention involves classes, we will recruit participants in nine cohorts consisting of 33 individuals each. We will recruit Group Health members who have made visits to their primary care physician for low back pain and whose pain has persisted for at least three months. However, if necessary to meet our recruitment goals, we will also advertise in Group Health's quarterly magazine.

A Group Health research programmer will use Group Health's electronic administrative and clinical databases to identify potentially eligible GHC members ages 20 through 64

years with a visit to a health care provider that resulted in a diagnosis consistent with low back pain.

Three months after their visit, potential participants will be mailed a letter and consent checklist that explains the study, clarifies eligibility requirements, and invites participation. Enrollees interested in participating will sign and return a statement indicating their willingness to be contacted by study staff. A Research Specialist will then phone interested enrollees to answer questions and determine eligibility using a computer program to guide the interviewer through a series of screening questions. The screening process ends with documentation in a database of either provisional eligibility or ineligibility. The Research Specialist will then review the consent checklist to administer informed consent. This will include an explanation of interview time commitments and content, intervention commitments (class attendance, home practice, and home practice diary completion), potential risks of participation, potential benefits of participation, what to do for an adverse event, and options for discontinuation of participation in the study. The Research Specialist will also explain the handling of data and personal health information as dictated by HIPAA. After informed consent has been administered the final eligibility confirmation and baseline telephone interview will be conducted. The Research Specialist will answer any remaining questions, collect baseline data and randomize the participant to one of our study groups.

If recruitment is slower than expected, we will place an ad in Group Health Cooperative's quarterly publication for enrollees entitled, *NWHealth*. This procedure has been successfully used in three previous studies for low back pain. The ad will contain study contact information so that interested enrollees can contact the study team for further details. Once an interested enrollee has contacted the study, the process will be the same as detailed above and the phone call will be analogous to returning the study postcard.

If the first contact with the potential participant takes place more than 14 days prior to the start of the cohort, approximately two weeks before the start of the cohort the participants will be called by a Research Specialist to reconfirm the presence of moderate levels of pain and activity limitations by re-administering the back pain bothersomeness and pain intensity scales. Persons answering at least a 4 on the bothersomeness scale and having a score of at least 3 on a 0 to 10 Pain Interference Scale will be coded as eligible in the study database and asked to join our study.

3.5 Random Assignment to Treatment

After completing the baseline assessment, participants will be randomized, in equal proportions to the MBSR, CBT, and Usual Care groups. Those randomized to MBSR or CBT will not be informed of their class assignments until they arrive at the facility on the night of the first classes, which will occur simultaneously in the same building. Intervention group will be assigned by a computer-generated sequence of random numbers using a program that ensures allocation cannot be changed after randomization. To ensure balance on a key baseline prognostic factor, randomization will be stratified on our primary outcome measure of dysfunction, the modified version of the Roland Disability Questionnaire (the "Roland"). We will stratify participants into two physical disability groups: *moderate* (Roland scores of 12 or less on the 0-23 scale) and *high* (Roland scores ≥13). Individuals with low levels of activity limitations will already

have been excluded prior to enrollment using the efficient single-item 0 to 10 pain interference scale (see Section 3.3). Participants will be randomized within these strata in blocks of varying size (three, six, or nine) to ensure balanced, but unpredictable, assignment of participants. The study biostatistician will remain blinded to the results by outcome. She will only receive aggregated counts of participants randomized to each group to assure that the pre-programmed randomization program is functioning properly.

3.6 Study Treatments

Mindfulness-Based Stress Reduction (MBSR): This 30-year old program has been well described in the literature. A recent meta-analysis found MBSR had moderate effect sizes for improving the physical and mental well-being of patients with a variety of conditions. It has been hypothesized that practicing mindfulness skills improves one's ability to experience pain without excessive emotional reactivity, leads to cognitive changes, and promotes relaxation. The eight weekly 2-hour MBSR sessions will include: 1) education about the concept of mindfulness, 2) instruction in becoming aware of one's breath), 3) examination of the relationship between perceptions and reality and discussion of ways to creatively respond to perceptions that make life more difficult, 4) instruction in techniques to help increase awareness of body sensations (e.g., body scan and yoga/mindful movement), 5) instruction in techniques intended to help develop a mindful practice (gentle yoga poses, walking meditation, guided meditation), 6) education about the concept of being present and living in the moment rather than in the past or future, 7) discussion of ideas for bringing more pleasant activities into one's life, 8) discussion of how we can get stuck in old patterns and of ways to break free from habitual patterns in the way we think, act, and react, 9) understanding stress, how to identify it and how to change how we react to it, 10) discussion of the connections between stress and pain, 11) exploration of strategies to cope with life's difficulties, and 12) education about how we communicate and learning ways to respond (and not automatically react) to difficult situations, people, or sensations. Participants will be given a packet of information at the first session that includes: class outline and instructor contact information, information about mindfulness, meditation, effects of stress on body/emotions/behavior, communications skills; homework assignments, poems, local resources, and a bibliography. All sessions will include mindfulness exercises, and all but the first will include yoga or other forms of mindful movement. Participants will also be given recordings (CDs or digital recordings) of the mindfulness and yoga techniques. Participants will be asked to practice the techniques discussed in each session daily for up to 45 minutes, throughout the intervention period, and after classes end. They will be also assigned readings to complete for each session. Time will be devoted in each session to a review of challenges that participants had in practicing what they had learned in class and with their homework. An optional Day of Practice will be scheduled between the 6th and 7th classes. This usually occurs over a six-hour period on a Saturday and is held in silence, with only the instructor speaking. This "retreat" will provide participants an opportunity to deepen what they learn in class.

Cognitive Behavioral Therapy (CBT): CBT for chronic pain has been well-described and found to be modestly to moderately effective in improving chronic pain problems. There is no single standardized CBT intervention for chronic pain, although all CBT interventions are based on the assumption that both cognitions and behaviors affect one's ability to adapt to chronic pain, and that maladaptive cognitions and behaviors can be identified and changed to improve pain and associated problems. CBT emphasizes active, structured techniques to teach patients how to identify, monitor and change maladaptive thoughts, feelings, and behaviors; a focus on helping patients acquire skills they can apply to a variety of problems; and a collaboration between the patient and therapist. A variety of techniques are taught, including training in pain and stress coping skills (e.g., use of positive coping self-statements, distraction, and problem-solving). CBT also promotes setting and working towards behavioral goals and identifying, evaluating, and correcting negative and dysfunctional thoughts.

Both individual and group formats have been used for CBT, and group CBT is often an important component of pain treatment programs. We will use a group CBT format because it has been found effective, is more resource efficient than individual therapy (an increasingly important concern), and provides patients with the potential benefits deriving from contact with, and support and encouragement from, others with similar experiences and problems. In addition, using group formats for both MBSR and CBT will eliminate intervention format as a possible explanation of any differences observed between the two therapies. The CBT intervention will consist of eight weekly 2-hour sessions that provide: 1) education about the role of maladaptive automatic thoughts (e.g., catastrophizing) and beliefs (e.g., one's ability to control pain, hurt equals harm) in chronic pain, depression, and anxiety; and 2) instruction and practice in identifying and challenging negative thoughts, thought-stopping techniques, use of positive coping self-statements, goal-setting, relaxation techniques, and coping with pain flare-ups. The intervention will also include education about activity pacing and scheduling, and about relapse prevention and maintenance of gains. Participants will be given recordings of relaxation and imagery exercises and asked to set goals regarding their relaxation practice. In each session, participants will fill out a "Personal Pain Coping Plan" for activities to be completed between sessions. These plans will be used as logs for checking off activities completed during the week to be reviewed at the next week's session.

Study participants will be encouraged to regularly practice the CBT techniques on their own. We will recommend participants in CBT to practice techniques daily, and will encourage each person to set their own goals around practice. To facilitate this we will encourage participants to set weekly action plans and will include 10 copies of the action plan in the participant workbook to help support their efforts; participants will be encouraged to make additional copies for personal use. Participants also will be encouraged to develop their own practice for 1) relaxation (e.g., diaphragmatic breathing, progressive muscle relaxation, body scan and/or guided imagery), 2) physical and pleasant activity goal-setting, 3) completing 4-column thought records, 4) using coping strategies, 5) pacing, and 6) managing flare-ups. Furthermore, proactive problem solving is conducted in Session 8 to help participants set short- and long-term goals with recognition of potential roadblocks to implementation, as well as a plan to return to practice if they should stop using them.

Session	CBT	MBSR
1	Rationale and evidence base for CBT, behavioral goal setting, introduction to relaxation techniques and Personal Pain Coping Plan	Setting expectations, definition of mindfulness, mindfulness exercise, movement, abdominal breathing instruction, introduction to home practice
2	Identifying and evaluating automatic thoughts related to pain, setting and working towards behavioral goals, relaxation	Perception and responding creatively to perceptions, yoga, body scan, discussion of developing a practice
3	Challenging automatic thoughts related to pain, setting and working towards behavioral goals, relaxation	The pleasure and power of being present, yoga, walking meditation, how to bring more pleasant events into our lives
4	Thought stopping and coping self-statements, identifying and challenging negative thoughts setting and working towards behavioral goals, relaxation	Getting unstuck from old patterns, yoga/movement, sitting meditation, stress (define, identify, how and why we stay stuck), dealing with pain
5	Activity pacing and scheduling, identifying and challenging negative thoughts, setting and working towards behavioral goals, relaxation	Reacting and responding differently to stress, yoga, guided meditation, establishing coping strategies (living with difficulties)
6	Core beliefs about pain, effective communication, identifying and challenging negative thoughts, setting and working towards behavioral goals, relaxation	Learning about communication patterns, yoga/meditation, styles of communicating with others (effective and ineffective)
7	Rehearsal of pain coping skills, coping with flare-ups, identifying and challenging negative thoughts, setting and working towards behavioral goals, mini-relaxation	Integrating the learning from the techniques, yoga/meditation, practical ways to bring mindfulness into daily life
8	Maintenance of coping skills, relapse prevention, personal plan for the future	This is the rest of your life, review mindfulness techniques/applications, closure

Usual Care: The Usual Care group will receive whatever care they would normally receive during the study period. Usual care for chronic back pain most often includes continued use of medications (mostly non-steroidal anti-inflammatory medications) and visits to primary care physicians, physical therapists, and CAM providers. A substantial fraction of persons with chronic back pain rely on self-care, only occasionally seeking professional help. In order to minimize disappointment at not being randomized to a mind-body treatment, participants in the Usual Care group will receive $50 compensation. This approach has helped maintain high response rates (i.e., close to 90%) from control group participants in our previous trials.

Class Sites: The CBT and MBSR classes will be offered in large, quiet classrooms at Group Health facilities that are centrally located and that provide easy access for persons with physical limitations.

3.7 Study Instructors: MBSR training will be provided by two Masters level psychotherapists. Both have received training from Dr. Kabat-Zinn's teacher training program at the Center for Mindfulness at the University of Massachusetts, have taught at least 20 MBSR courses, have worked with Group Health patients, and have had a personal meditation practice for over 15 years. Two PhD-level clinical psychologists with previous experience conducting CBT with patients with chronic pain will provide the CBT intervention. Drs. Turner and Balderson will thoroughly train the psychologists to conduct the CBT groups.

3.8. Participant Retention and Adherence

A Research Assistant from the study will monitor class attendance in the 8-week CBT and MBSR classes. Participants will receive a reminder call before the first class and whenever they miss any classes. The investigators will use this information to document adherence with these interventions.

During each class, participants will be reminded of the importance of attending classes and of practicing at home. A portion of each class will be devoted to answering questions that arise during home practice and, if necessary, to exploring any perceived barriers to adherence. To monitor adherence with the home practice assigned by the CBT and MBSR instructors we will also ask participants to record their daily home practice on weekly logs. To facilitate accurate reporting of home practice, a study Research Assistant will collect the home practice logs at the beginning of each class. The logs will not be shown to the class instructors. Questions about practice in the prior week will also be included in all follow-up interviews. To maintain interviewer blinding, adherence questions will be asked only after all outcomes data are recorded.

To optimize response rates on the follow-up assessments, we will send advance letters before the all follow-up interviews reminding participants they will be called and we will also compensate them $20 for their time in completing each of the follow-up interviews. This approach has worked well in our previous studies of yoga, acupuncture, and massage.

There are a variety of conceivable reasons participants may prematurely discontinue the class series and study staff will use the following groupings to categorize them:

- Practice of CBT or MBSR associated with unacceptable or serious adverse experiences from perspective of participant
- Continued participation considered inadvisable by investigator, class instructor or participant's physician due to concerns that continued participation poses an unacceptable risk to the patient.
- Participants do not care for the class environment
- Interventions perceived as ineffective by participant
- Events in participant's life unrelated to trial (e.g., illness or death in family)

A study withdrawal form will be completed for individual who discontinues the intervention. In all cases, participants who discontinue treatments will be encouraged to complete the remaining follow-up interviews.

4. DATA COLLECTION, QUALITY CONTROL AND CONFIDENTIALITY

Data will be collected from participants by trained telephone interviewers at baseline, about midway through the treatment period (4 weeks after randomization), 8 weeks after randomization (just after the classes have ended), and 26 and 52 weeks after randomization. Reminder letters will be sent before each follow-up interview. Interviewers will be blinded to participants' treatment assignments. Interview data will be collected with a computer-assisted telephone interview (CATI) version of the questionnaires to minimize errors and missing data. Questions about experiences with specific aspects of the interventions (e.g., yoga, meditation, instruction in coping strategies) that would unmask interviewers to treatment group will be asked at the end of an interview, after all other outcomes are assessed. We will attempt to obtain outcome data from all participants in the trial, including those who never attend or who drop out of the classes, who discontinue enrollment in the health plan, and who move away. We will send participants $20 after each interview completed to maximize response rates.

We will collect information at every stage of recruitment, randomization, and treatment so we can report patient flow according to the CONSORT guidelines. We will adapt our standard quality control procedures to monitor the trial, verify accuracy of data collection and analyses, and ensure patient confidentiality

We will implement procedures to ensure that all data collection processes are proceeding smoothly. These procedures will ensure that randomization is proceeding as planned, recruitment is on schedule, data collection forms are accurately entered into databases, the computerized assisted telephone interviewing (CATI) system is storing data correctly and that data can be accurately transferred and retrieved as needed. We will develop a relational database to track information on every stage of recruitment, randomization, class attendance, and outcomes assessment so we can report patient flow automatically and in an integrated fashion using standard, automated reports. All data system processes will be thoroughly tested prior to the start of recruitment.

The computerized interviewing programs will contain range and logic checks. Participant attendance information collected during the classes will be double key entered into a computer database that also contains logic checks. Prior to recruitment, all data systems will be tested with imaginary participants. Data will be examined for

completeness using computer programs developed specifically for that purpose. In addition, we will test all analytic programs to ensure that the analyses are accurate.

To maintain the confidentiality of patient-related information in the database, unique participant study numbers will be used to identify patient outcomes and treatment data. The password security system will assign appropriate levels of computer privileges to different groups of database users. This will ensure that all masked personnel remain masked to treatment group.

Computer files with participant names will be password protected with access restricted to staff using this information to recruit participants, contact class participants or obtain follow-up data, and interact with any patients reporting adverse events. Any paper data forms, such as homework logs, identifiable only by unique study ID numbers, will be kept in locked filing cabinets. Finally, all analysis data files will be password protected. Full data backup procedures are performed nightly, with partial data back-up throughout the day.

5. TRAINING AND MONITORING OF CLASS INSTRUCTORS

MBSR training will be provided by two Masters level psychotherapists. Both have received training from Dr. Kabat-Zinn's teacher training program at the Center for Mindfulness at the University of Massachusetts, have taught at least 20 MBSR courses, have worked with Group Health patients, and have had a personal meditation practice for over 15 years. Two PhD-level clinical psychologists with previous experience conducting CBT with patients with chronic pain will provide the CBT intervention. Drs. Turner and Balderson will thoroughly train the psychologists to conduct the CBT groups.

During the class series, Drs. Balderson, Sherman and Turner will be in weekly contact with the instructors and will inquire about positive experiences, adverse events, concerns raised by participants, ability to stay within the protocol, and any other questions that may arise. Research Assistants will attend each of the classes to collect home practice information and take attendance. Treatment fidelity will be monitored in the MBSR classes by Dr. Sherman and the Research Specialists. Dr. Sherman will attend the first class of every session and complete the treatment monitoring and fidelity checklist. Subsequent classes will be monitored by Research Specialists trained by Dr. Sherman. Treatment fidelity will be monitored in the CBT classes by Drs. Balderson and Turner and the Research Specialists. Dr. Balderson or Dr. Turner will attend the first class of every session and complete the treatment monitoring and fidelity checklist. Subsequent classes will be monitored by Research Specialists trained by Dr. Turner.

6. ASSESSMENT OF OUTCOMES

We will assess a variety of baseline characteristics including sociodemographic characteristics (gender, age, race, ethnicity, education level, employment status, and marital status), back pain history (e.g., years since first episode of back pain, duration of current episode) and other factors that are prognostic of resolution of back pain (e.g., number of pain sites and patient expectations of treatment outcome). We will ask participants assigned to one of the two mind-body interventions about their expectations of the helpfulness of the mind-body treatments for back pain and the perceived.

Content of Baseline and Follow-up Questionnaires

SOURCES OF DATA FOR MAP TRIAL

MEASURES	Base-line Q	4 wk Q	8 wk Q	26 wk Q	52 wk Q
BASELINE CHARACTERISTICS					
Patient characteristics (education, race, ethnicity, marital status, income, work status, # of pain sites) *(age, gender from EMR)*	x				
Back pain (pain duration, interference with activities, days of pain in past 6 months, previous spinal injections, radiates below knee)	x				
Expectations for back pain improvement: 1) in general, 2) as result of mind-body program	x				
PRIMARY OUTCOMES					
Back pain-related dysfunction (modified Roland scale)	x	x	x	x	x
Bothersomeness of back pain (0-10 scale)	x	x	x	x	x
SECONDARY OUTCOMES					
Characteristic pain intensity (GCPS) (average: pain now, worst pain, average pain)	x		x	x	x
Depression (PHQ-8)	x		x	x	x
Anxiety (GAD-2)	x		x	x	x
LBP-related medications used in past week	x		x	x	x
Exercise in past week (LBP-specific and general)	x		x	x	x
Global improvement (PGIC)			x	x	x
Program's impact on thoughts, feelings, reactions, activities (open ended)			x	x	x
EXPLORATORY OUTCOMES: POTENTIAL MEDIATORS					
MBSR: Mindfulness (FFMQ-SF), Pain Acceptance (CPAQ-8)	x	x	x	x	x
CBT: Pain beliefs/appraisals (PSEQ; SOPA 2-item Control, Disability, Harm, Emotion scales; PCS), Pain coping strategies (CPCI 2-item relaxation scale, Activity Pacing scale)	x	x	x	x	x
EXPLORATORY OUTCOMES: COST-EFFECTIVENESS ANALYSES					
Quality of life (EQ-5D, SF-6D from the SF-12)	x	x	x	x	x
Out of plan visits paid for by patients since previous follow-up interview	x		x	x	x
Absenteeism, Presenteeism (WPAI-CLBP)	x		x	x	x
Costs paid by Group Health (payer) for back-related utilization of services (visits, tests, Rx) and total costs.	*From electronic medical records for year prior to trial and for follow-up year.*				
INTERVENTION-RELATED INFORMATION					
Class attendance		Class Records			
Adverse experiences from classes or home practice		X	X	X	X
New serious health problems since entering study?		X	X	X	X
Self-reported home practice		X	X	X	X
Perceived helpfulness of classes/home practice			X	X	X
Would recommend program to friends			X	X	X

Abbreviations: CPAQ=Chronic Pain Acceptance Questionnaire; CPCI=Chronic Pain Coping Inventory; EQ-5D=European Quality of Life Instrument; FFMQ=Five-Facet Mindfulness Questionnaire; GAD=Generalized Anxiety Disorder scale; GCPS=Graded Chronic Pain Scale; PCS=Pain Catastrophizing Scale; PGIC=Patient Global Impression of Change; PHQ=Patient Health Questionnaire; PSEQ=Patient Self-Efficacy Questionnaire; SF-12=Medical Outcomes Study, Short-Form 12; SOPA=Survey of Pain Attitudes; WPAI-CLBP=Work Productivity and Activity Impairment Questionnaire-Chronic Low Back Pain.

We will measure a core set of recommended outcomes for spinal disorders (back–related function, pain, general health status, work disability and patient satisfaction) that are consistent with the IMMPACT recommendations for clinical trials of chronic pain treatment efficacy and effectiveness. We will measure outcomes after completion of the interventions (8 weeks) and again after 26 and 52 weeks to determine if any short-term benefits persisted or increased and if participants continued to practice their new skills.

In addition, a brief 4-week mid-treatment assessment will focus on collecting data for the analyses of the hypothesized mediators of the effects of MBSR and CBT on the primary outcomes. The primary study endpoint is 26 weeks.

6.1 Co-Primary Outcome Measures

Back-related dysfunction will be measured with the modified Roland Disability Questionnaire ("Roland scale") which asks whether 23 specific activities were limited due to back pain during the past week (yes or no). This measure has been found to be reliable, valid and sensitive to clinical changes, and is appropriate for telephone administration and patients with moderate disability.

Symptom bothersomeness will be measured by asking participants to rate how "bothersome" their back pain has been during the previous week on a 0 to 10 scale (0 = "not at all bothersome" and 10 = "extremely bothersome"). This question worked well in our previous trials and is highly correlated with a 0-10 measure of pain intensity (r=0.8 to 0.9). It is also highly correlated with measures of function and other outcome measures. The validity of numerical rating scales of pain has been well documented, and such scales have demonstrated sensitivity to detecting change in pain after treatment.

We will analyze and report these co-primary outcomes in two ways. First, for our primary endpoint analyses, we will compare the percentages of participants in the three treatment groups who achieve clinically meaningful improvement (at least 30% improvement from baseline) in each time point with 26-week follow-up the primary time point. We will then examine, as a secondary outcome analysis, the adjusted mean differences between groups on these measures at follow-up.

6.2 Secondary Outcomes:

Depression will be assessed with the Patient Health Questionnaire-8 (PHQ-8) which measures both depression severity and current DSM-IV depression diagnostic status. With the exception of the elimination of a question about suicidal ideation, the PHQ-8 is identical to the PHQ-9, which has been found reliable, valid, and responsive to change.

Anxiety will be measured with the 7-item Generalized Anxiety Disorder scale (GAD-7), which has demonstrated good reliability and validity in primary care populations and in the general population.

Pain Interference with normal daily activities will be measured with 3 items from the Graded Chronic Pain Scale (GCPS). The GCPS has been validated and shown to have good psychometric properties in a large population survey and in large samples of primary care patients with pain. We will use the three items that ask participants to rate, on 0 - 10 scales, their degree of pain interference with daily activities, work/housework activities, and recreational/social activities in the past week. The mean of these three ratings has good internal consistency (.89), test-retest reliability (.85 over a 1-2 week interval), and validity, as evidenced by associations with other measures of pain severity and disability.

Global improvement with treatment will be measured with the Patient Global Impression of Change scale. This single question asks participants to rate their

improvement with treatment on a 7-point scale that ranges from “very much improved” to “very much worse,” with “no change” as the mid-point. Global ratings of improvement with treatment provide a measure of the overall clinical benefit from the treatment and are considered one of the core outcome domains for pain clinical trials.

Use of back-related medications and exercise in past week will be measured on the 8, 26 and 52-week questionnaires to provide an indication of how these behaviors were affected by the interventions. They also provide an indication of “co-interventions” that occurred during the follow-up period.

General health status will be measured with the SF- 12, a widely used instrument that yields summary scores for physical and mental health status. The SF-12 will also be used to calculate quality-adjusted life-years (QALYs) using the SF-6D in the cost-effectiveness analyses.

Qualitative outcomes: Inclusion of open-ended questions in our previous trials has yielded valuable insights into participants’ feelings about the value of specific components of the interventions and the impact of the interventions on their lives. We will, therefore, include open-ended questions asking about these issues at the end of the 8, 26 and 52-week follow-up interviews.

6.3 Exploratory Outcomes

6.31 Potential Mediators: For MBSR, we will evaluate the mediating effects of increased mindfulness (measured by the Five Facet Mindfulness Questionnaire) and pain acceptance (measured by the Chronic Pain Acceptance Questionnaire) on the primary outcomes of. For CBT we will evaluate the mediating effects of improvements in pain beliefs/appraisals (measured by the Patient Self-Efficacy Questionnaire; the Survey of Pain Attitudes Control, Disability , Harm, and Emotion Scales; and the Pain Catastrophizing Scale) and improvements in pain coping strategies (measured by the Chronic Pain Coping Inventory’s Relaxation and Activity Pacing scales). Although we expect the effects of MBSR and CBT on outcomes to be mediated by different variables, we will explore the effects of all potential mediators on outcomes for both treatment groups.

6.32. Cost and Effectiveness (Utility) Measures. Costs will be estimated using cost data from the electronic medical records for back-related services provided or paid by Group Health. The effectiveness of the intervention will be derived from the SF-12 general health status measure.

7. ASSESSMENT OF SAFETY

7.1 Adverse Events

We will collect data on adverse experiences from several sources and incorporate them into a database. These sources are: 1) reports from the CBT and MBSR instructors of any extraordinary occurrences of concern to them, 2) the computer-assisted telephone-administered 4 and 8, 26 and 52-week follow-up questionnaires will inquire about: any harm they felt from the CBT or MBSR treatments, and any serious health problems, and 3) participants themselves because the consent form directs participants with injuries they believe may be related to the mind-body programs to call the Principal Investigator, Co-Investigators or the Human Subjects

Representative, whose names and phone numbers are listed on the copy of the consent form retained by the participant. Adverse experience data from the questionnaires will be provided to the Project Manager within a week (and will be transferred to the AE database). These will be reviewed, as will AE reports from all sources, by Dr. Sherman, with the assistance of Co-Investigator Balderson (a psychologist) and GHRI physician Kathy Bradley (a primary care internist) on a weekly basis and any Serious Adverse Experiences identified will be reported promptly to the Group Health HSRC and the DSM Body. If an adverse event is reported by phone, the study staff member will complete an Adverse Events form, which will be entered into the database and will alert Project Manager Hawkes and Co-I Sherman of the new AE report. If a Serious Adverse Experience is identified by phone, it will be reported as outlined below. Adverse experiences that are not serious will be recorded and included in regular DSM Body reports, but will not be reported early to the DSM Body. Appendix A details adverse event reporting as required by the Group Health IRB.

Serious Adverse Events that are fatal will be reported to the DSM Body chair within 7 days of discovery, regardless of attribution. The table below details the adverse event reporting schedule and actions:

Adverse Event	**Action taking by study team** (Timeframes for reporting to GH HSRC are described in Appendix AI)
Serious	
Fatal	
CBT/MBSR Related[a]	Record on AE and SAE forms Report to DSM Body Chair within 3 days of discovery
Not CBT/MBSR Related[b]	Record on AE form Report to DSM Body within 7 days of discovery
Not Fatal	
CBT/MBSR Related[a]	Report on AE and SAE forms Report to DSM Body within 7 days of discovery
Not CBT/MBSR Related[b]	Record on AE form Report to DSM Body as part of regular reports
Not Serious	Record on AE form Report to DSM Body and IRB as part of regular reports

[a] possibly, probably or definitely
[b] definitely not

7.2 Safety Monitoring Body

This is an unmasked Phase II trial comparing CBT, MBSR, and Usual Care for chronic back pain. Given the favorable safety profile from previous studies of CBT and MBSR including our own coupled with the small numbers of adverse events reported in the literature, this trial will be monitored for safety by an independent Data Safety Monitor Body (DSMBody) comprised of a primary care physician experienced in mindfulness, a biostatistician, and a pain psychologist.. The DSMBody's job will be to evaluate the adverse-experience data we will provide them on a regular basis to protect the safety of the study participants. Based on the observed adverse effects of the treatment under study, the SMB will make recommendations on a regular basis to the PI and the Office of Clinical and Regulatory Affairs at the National Center for Complementary and Alternative Medicine (NCCAM) regarding continuation, termination, or other modifications of the trial.

8. STOPPING RULES

The trial will be stopped only if the Safety Monitoring Body (SMB) believes there is an unacceptable risk of serious adverse events in one or more of the treatment arms. In this case, the SMB could decide to terminate one of the arms of the trial or the entire trial. Based on our previous research and on the small number of reports of adverse events from these treatments reported in the literature, we believe the risk of serious adverse events related to our CBT and MBSR interventions is quite small.

9. STATISTICAL ISSUES

9.1. Sample Size and the Detectable Difference Our sample was chosen to ensure adequate power to detect a significant difference between each of the two mind-body treatment groups and the Usual Care group, as well as power to detect a difference between the two mind-body treatment groups. Because we consider patient function (or dysfunction) the more consequential of our two primary outcome measures (the other being bothersomeness of back pain), we base our sample size calculations on the modified Roland Disability Questionnaire. We specify our sample size based on the expected percentage of patients with a clinically meaningful improvement on the Roland Score of at least 30% (relative to baseline) at the 26 week follow-up measure.

To protect against multiple comparisons, we will use Fisher's protected least significance approach, first testing if there is any significant difference among all 3 groups (using the omnibus Chi-Square Likelihood Ratio test). If we find a difference, we will then test for pairwise differences between groups. We will need 264 participants (88 in each group) to achieve 90% power to find either mind-body treatment different from Usual Care. This assumes that 30% of the Usual Care group and 55% of each mind body treatment group will have clinically meaningful improvement at 26 weeks, rates of improvement that are similar to those we observed in a similar back pain population in two studies (one not yet published) evaluating CAM treatments for back pain. Finally, we will have at least 80% power to detect a significant difference between MBSR and CBT if MBSR is at least 21% more effective than CBT (i.e., 76% of the

MBSR group versus 55% of the CBT group).

Our other co-primary outcome is improvement from baseline on the Bothersomeness Score. With a total sample size of 264 participants, we will have 80% power to find a mind-body treatment group different from Usual Care assuming that 47.5% of Usual Care and 69.3% of the mind body treatment groups have 30% or more improvement in the bothersomeness score from baseline.

When analyzing the primary outcomes as continuous measures, we will have 90% power to detect a 2.95 point difference in the modified Roland Score and a 1.78 point difference in Bothersomeness score (assumes normal approximation to compare two independent means with equal variances, a two-sided, 0.05 test with standard deviations of 6.0 and 2.4 for Roland and Bothersomeness, respectively (unpublished data from current study of massage for chronic back pain). Thus, we will have ample power for detecting clinically meaningful differences since differences of 2.5 on the Roland scale and 1.5 on the bothersomeness scale are considered clinically meaningful. Assuming 11% loss to follow-up (slightly higher than was found in our previous back pain trials), we plan to recruit a total sample size of 297 participants (99 per group).

Both co-primary outcomes will be tested at the $p < 0.05$ level at each time point because they address separate scientific questions. Analyses of both outcomes at all follow-up times will be reported, imposing a more stringent requirement than simply reporting a sole significant outcome.

9.2 Statistical Analysis

In our comparisons of treatments on the outcome measures, we will analyze outcomes from all follow-up time points in a single model, adjusting for possible correlation within individuals and treatment group cohorts using generalized estimating equations (GEE). Because we cannot reasonably make an assumption of constant or linear group differences over time, we will include an interaction term between treatment group and time point. We plan to adjust for baseline outcome value, gender, and age as well as other baseline characteristics found to significantly differ by treatment group or follow-up outcomes to improve precision and power. We will conduct the following set of analyses for both the continuous outcome score and the binary outcome clinically significant change from baseline including all follow-up time points (4,8, 26, and 52 wks). However, since the primary time point is at 26 weeks the MBSR treatment will only be deemed successful if the 26 week time point comparisons are significant. The other time points are considered secondary evaluations.

We will use an intent-to-treat approach in all analyses; *i.e*., individuals will be analyzed by randomized group regardless of participation in any classes. This minimizes biases that often occur when participants not receiving assigned treatments are excluded from the analyses. The general form of the regression model will be:

$g(Y(t)) = \beta_0 + \beta_1 Baseline + \alpha_1 Trt + \alpha_2 Time + \alpha_3 Trt \times Time + \alpha_4 z + \varepsilon$, where $Y(t)$ is the response at follow-up time t, *Baseline* is the pre-randomization value of the outcome measure, *Trt* includes dummy variables for the MBSR and CBT groups, *Time* is a series of dummy variables indicating the follow-up times, and z is a vector of covariates

representing other variables being adjusted for. (Note that α_1, α_2, α_3, and α_4 are vectors.) The referent group in this model is the Usual Care group. For binary and continuous outcomes, we will use appropriate link functions (i.e., logit for binary). For each follow-up time point that the omnibus Chi-Square Score test is statistically significant, we will go on to test whether there is a difference between MBSR and Usual Care to address Aim 1 and a difference between MBSR and CBT to address Aim 2. We will also report the comparison of CBT to Usual Care. When determining that MBSR is an effective treatment for back-pain we will require that Aim 1, the comparison of MBSR to Usual Care, must be observed.

Based on our previous back pain trials, we expect at least 90% follow-up rate and so our primary analysis will be a complete case analysis including all observed follow-up outcomes, but we will adjust for all baseline covariates that are predictive of outcome, probability of being missing, or differences between treatment groups. By adjusting for these baseline covariates our model assumes that the missing outcome data are missing at random instead of missing completely at random. We will also conduct sensitivity analysis using an imputation method for non-ignorable non-response to evaluate whether our results are robust to different missing data assumptions

If MBSR or CBT is effective (relative to usual care and/or each other) in improving either primary outcome at 26 or 52 weeks, we will move to Aim 3 (to identify the mediators of the effects of MBSR and group CBT on pain-related functional limitations and pain bothersomeness). We will perform the series of mediation analyses separately for the two primary outcomes (Roland and pain bothersomeness) and for each separate treatment comparator of interest (usual care-CBT, usual care-MBSR, CBT-MBSR). We will conduct separate mediator analyses for the 26-week and 52-week outcomes (if MBSR or CBT is found effective at those timepoints). Below is the detailed description of the mediator analysis for the 26-week time-point, but a similar analysis will be conducted for the 52-week time-point.

We will apply the framework of the widely used approach of Baron and Kenny. Having demonstrated the association between the treatment and the outcome variable (the “total effect” of the treatment on the outcome), the second step will be to demonstrate the association between the treatment and each putative mediator. We will construct a regression model for each mediator with the 4 or 8-week score of the mediator as the dependent variable and baseline score of the mediator and treatment indicator as independent variables. We will conduct this for each potential mediator and only include those mediators that have at least a $P < 0.10$-level significant relationship with the treatment as potential mediators in the following step. The third step is to demonstrate the reduction of the treatment effect on the outcome after removing the effect of the mediator(s). We will construct a multi-mediator inverse probability weighted (IPW) regression model. This approach allows us to estimate the direct effect of treatment after rebalancing the treatment groups with respect to the mediators. The application of the IPW approach, as compared to the traditional approach of adjusting for multiple mediators, allows us to more appropriately account for confounding between a mediator and the outcome both by additional mediators and by other measured variables. Further, we are better able to estimate the indirect effects of each mediator in a causal framework through decomposition of the

total effect of treatment into indirect effects through each mediator and the direct effect after accounting for all mediators. Specifically, we will first model the probability of the treatment given the mediators (all mediators that were found associated with treatment in step 2) using logistic regression adjusting for potential baseline confounders. From this model we will obtain the estimated probabilities that each person received their observed treatment given their observed mediator value. We will then use an IPW regression to model the primary outcomes on treatment status while adjusting for the baseline level of the outcome and mediator. Comparing the weighted to the unweighted model will allow us to estimate how much of the direct effect of treatment on the outcome can be explained by each potential mediator. The inclusion in Step 3 of all mediators found to be significant in Step 2 will enable us to examine whether the specific variables we hypothesized to differentially mediate the effects of MBSR versus CBT in fact mediate the effects of each treatment, independently of the effects of the other "process variables".

9.3 Cost Effectiveness Analyses: A societal perspective cost-utility analysis (CUA) will be performed comparing the incremental societal costs for each treatment arm (direct medical costs paid by GHC and the participant plus productivity costs) to incremental effectiveness in terms of change in QALYs. This CUA can be used by policy makers concerned with the broad allocation of health resources. For the payer perspective, direct medical costs (including intervention costs) will be compared to change in QALYs. This CUA will help determine whether it makes economic sense for MBSR to be a reimbursed service for this population. A bootstrap methodology will be used to estimate confidence intervals. Secondary analyses to assess different cost outcome definitions such as varying assumptions of wage rates used to value productivity and the inclusion of non-back-related utilization in the total cost amounts will also be considered. Cost effectiveness analyses will use intention to treat and will adjust for health care utilization costs in year prior to enrollment and baseline variables that might be associated with treatment group or outcome, such as medication use, to control for potential confounders. We expect minimal missing data, but sensitivity analyses as described for the primary outcomes will also be performed for cost measures.

10. ORGANIZATION AND ADMINISTRATION

10.1 Funding and Organizational Oversight

The MAP study is a four-year single-site clinical trial currently funded as a R01 (NIH grant number AT 003208) by the National Center for Complementary and Alternative Medicine (NCCAM). Dr. John Glowa, the NCCAM Project Officer assigned to this project, provides NCCAM oversight on the project. A specially-created Safety Monitoring Body will ensure the safety and welfare of patients enrolled in this trial. Budgetary oversight will be provided by NCCAM staff. The study was reviewed and approved by NCCAM's Office of Clinical and Regulatory Affairs.

10.2 Organizational Structure

Administrative Leadership is based at the Group Health Research Institute in Seattle. Overall scientific and administrative responsibility for the project resides with Dr. Daniel Cherkin, the Principal Investigator. Ms. Rene Hawkes, Project Manager, is responsible for day-to-day project administration, human resources issues, correspondence with the IRB, supervision of study staff, and coordinating liaison with the CBT and MBSR class instructors. The biostatistician, Dr. Andrea Cook will have responsibility for ensuring data integrity. The Safety Monitoring Body will have responsible for ensuring the safety of study participants.

10.3 Publications Policies and Procedures

The Principal Investigator has responsibility for developing and maintaining a list of proposed publications including topic, names of the primary authors and date proposed. It is the first author's responsibility to determine who will be listed as co-authors and in what order. We will follow the International Committee of Medical Journal Editors' guidelines on authorship on all manuscripts deriving from this study. "Publications" will be a standing item on the agenda for team meetings to ensure open and frequent discussion of this issue. The P.I. will be first author on the primary manuscript, but first authorship on all other manuscripts will be shared.

11. ETHICAL PRINCIPLES

11.1 Informed Consent: Once a potential participant has been confirmed eligible, a study research specialist will ask the participant if he/she still has the Consent Checklist that was included with the mailed invitation letter. If the participant does not have the Consent Checklist, the Research Specialist will instruct the participant on how to access it on our study website. If the participant does not have internet access, the Research Specialist will mail another copy of the Consent Checklist to the participant, but will continue with the informed consent process. The Research Specialist will guide potential participants through the study consent and HIPAA processes. During the informed consent process, the Research Specialist will explain the study requirements. This will include an explanation of interview time commitments, intervention commitments (coming to 8 class sessions if randomized to CBT or MBSR and home practice expectations), potential risks of participation, potential benefits of participation, what to do for an adverse event, and options for discontinuation of participation in the study. The Research Specialist will also explain the handling of data and personal health information as dictated by HIPAA. Once informed consent has been administered, all questions have been answered, and the potential participant has agreed to take part in the study, the Research Specialist will document the informed consent in the study database. Participants randomized to one of our intervention arms will also be asked to sign a written consent form when they arrive for the first night of class. The Group Health IRB and our DSMB have approved this consenting process for this low-risk intervention and we have obtained a waiver of documentation of written consent from our IRB. All of our Research Specialists have been trained in the process of administering informed consent. The consent checklist contains information about HIPAA as described below.

11.2 Health Insurance Portability and Accountability Act (HIPAA)

Group Health Cooperative has instituted a protocol that ensures research is conducted in compliance with the federal law entitled, “Health Insurance Portability and Accountability Act (HIPAA)”. Permission to use, create, and release personal health information for research will be obtained before potential participants can be enrolled in this study. One of the study Research Specialists will explain HIPPA as it relates to this research study to potential participants to ensure that they understand it and have the opportunity to ask any questions pertaining to their personal health information as it relates to this study. This process will explain what is meant by health information, how health information is obtained, how the researchers may use health information, and detail the steps a participant must take if s/he decides to revoke this permission.

11.3 Institutional Review Board

The investigators are responsible for obtaining initial and continuing review (at intervals of not less than yearly) of the study by their IRB. Written approval from the IRB will be on file prior to commencement of study activities. All key study personnel have Human Subjects Research Training certification on file with the IRB.

11.4 Confidentiality of Participant Records

The investigators and their study teams will maintain strict confidentiality of the participant records. Individual records will be identified by a unique study identification number. Records linking study ID with participant names or other identifying information that may be needed for follow-up interviews, class attendance, etc. will be kept separate from the study data and will be accessed only by study team members on a need-to-know basis. All study files will be kept in a locked filing cabinet. Computer files will be secure and password protected.

12. STUDY TIMELINE

During a 6-month start-up period, we will recruit and train study staff, complete documentation of the study protocol and submit it to the IRB and NCCAM, finalize the MBSR and CBT intervention protocol, develop the training materials used for the CBT and MBSR class teachers and refine the homework materials for class participants. We will also build the appropriate databases, develop and test the randomization procedure, and develop and test the protocol for the data quality control procedures. During months 7-30, we will recruit and randomize 9 successive cohorts of participants. The interventions will occur during months 10-33. All participants will be followed for 12 months post-enrollment. Homework logs collected at class sessions will be scanned into databases on an ongoing basis and computerized interview data will be collected throughout months 7-36. Extraction of automated visit data will occur one year after the last participant is randomized. Data analysis and manuscript preparation will occur during months 37-42.

13. References

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Appendix A: Group Health IRB (Human Subjects Review Committee – HSRC) Reporting Requirements related to Adverse Events

Principal Investigator Reports to HSRC:	Report Within 1 Business Day	Report within 15 Days of Rect or before next HSRC Meeting Deadline (whichever is first)	Report at PI Discretion	Summarize at Continuing Review
Adverse Events (AE)				
Unexpected death of research participant that is at least possibly related to the study	✓			✓
Unexpected death of research participant that is not related to the study				✓
Adverse Events which are unexpected, serious, and at least possibly related to the study—(these AE's also represent Unanticipated Problems)		✓		✓
Unexpected and serious, but definitely not related to the study, and not an Unanticipated Problem				✓
Serious Adverse Events that are expected (see definition) in some subjects, but are determined or suspected to be occurring at a significantly higher frequency or severity than expected.		✓		✓
Expected (see definition) adverse events, serious or not serious, at least possibly related, not occurring at a higher frequency or severity than expected				✓
Any event leading to the PI's concern regarding health, safety, or rights of research participants		✓		✓
Other Unexpected Adverse Events, regardless of severity, that may alter the HSRC's analysis of the risk versus potential benefit of the research because they suggest that the research places subjects or others at greater risk of physical or psychological harm than was previously known or recognized and, as a result, may warrant consideration of substantive changes in the research protocol or informed consent process / document.		✓		✓
Summarize **ALL** Adverse Events (whether previously reported to HSRC or not) at time of yearly continuation review)				✓

If DSM Body determines that an Adverse Event that was not previously reported to the HSRC, is now determined to also represent an Unanticipated Problem (for example due to increased frequency), then the Investigator must report it promptly to the HSRC. Include the monitoring entity's report with any actions taken with the submission to the HSRC. In addition, summarize the event(s) at time of Continuing Review.