

1) Protocol Title

The Effect of Mindfulness-Based Stress Reduction on Pain and Function in Persons with Knee Osteoarthritis

Protocol Version Date: April 3, 2018

2) Study Aims

Our goals are to establish feasibility of a controlled trial at UC Davis comparing the effects of Mindfulness-Based Stress Reduction (MBSR) versus online MBSR versus an active comparison Health Enhancement Program (HEP) (Aim 1) on measures of pain and function in persons with knee osteoarthritis (OA) (Aim 2), and to collect preliminary data on the effect of MBSR on serum stress and inflammatory markers (Aim 3). This pilot study will be complete in one year.

Specific Aim 1: To determine the feasibility of enrolling symptomatic knee OA patients and performing a non-randomized study comparing MBSR vs online MBSR vs HEP.

Hypotheses 1: It will be possible in the UC Davis Medical System to enroll knee OA patients and perform an RCT.

Specific Aim 2: Compare the effect of MBSR vs online MBSR vs HEP on pain and function limitations in knee OA.

Hypothesis 2: Compared with HEP, MBSR will result in significantly greater improvement in pain intensity and function.

Specific Aim 3: Investigate whether MBSR and online MBSR result in decreases in serum cortisol level or changes in eicosanoid parameters compared with HEP intervention.

Hypothesis 4: MBSR will result in decreases in serum cortisol level and changes in eicosanoid parameters compared with HEP intervention.

3) Background

Rationale: Current treatments for OA and pain in OA all are non-ideal. Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with a high risk of gastrointestinal bleeding and cardiovascular events^{1,2} and are only moderately effective for treating pain, while opiates and surgery carry other risks. There is evidence that interventions affecting emotional state may moderate pain in OA, both in our work and elsewhere³⁻⁵. MBSR⁶ is a secular program that trains mindfulness meditation for stress reduction and to increase emotional regulation skills. Meta-analyses of mindfulness-based interventions (MBIs) have demonstrated reliable clinical efficacy, specifically in the reduction of symptoms of stress, depression and anxiety⁷. A recent meta-analysis of MBIs for non-OA chronic pain patients determined that mindfulness meditation is associated with decreases in pain, as well as improvement in depression and quality

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of life compared with all types of control conditions⁸. To our knowledge, there are no prior peer-reviewed studies that answer whether an MBSR intervention improves pain or function in knee OA.

Research is needed to investigate the relation of mindfulness practices with stress hormones and markers of inflammation. Prior studies investigating the effect of mindfulness interventions on changes in the level of the stress hormone cortisol conflict, with some studies showing no effect and others demonstrating significant changes with mindfulness training^{9,10}; one study of a short-term MBI demonstrated reductions over 10 days of the intervention in levels of inflammatory cytokines interleukin-6 and TNF-alpha¹¹.

Preliminary data - MBSR effect on pain and cognitive reappraisal in adults with primary anxiety disorders: In a sample of 39 adults with primary anxiety disorders, we found that standard MBSR produced significant decreases in Patient Reported Outcomes Measurement Information System (PROMIS) measures of pain intensity ($p < .001$) and interference ($p < .001$). This confirms that MBSR reduces pain experience in anxiety disorder patients with a variety of secondary pain problems.

Description of intervention and comparator: The intervention will be MBSR as described above. The online MBSR course will be offered through: <http://www.breathworks-mindfulness.org.uk/mindfulness-for-health>. We propose to use an active control training, the Health Enhancement Program (HEP), an intervention designed to isolate mindfulness as a testable active ingredient¹². HEP and MBSR are structurally equivalent, both using a group format that meets once a week for 2.5 hours for 8 weeks with an “all day” component after week 6, plus home participation. The content of the HEP intervention meet the following criteria: (1) class activities match MBSR activities as closely as possible, (2) activities represent valid, active, therapeutic ingredients in their own right, and (3) these ingredients do not include mindfulness. We will also measure steroid and oxylipin inflammation markers through the UC Davis designated metabolomics core at baseline and end of intervention.

Description of outcome measures: Participants will be asked at each time point to complete a validated, widely-used disease- and joint-specific questionnaire-based knee OA symptom evaluation, the Western Ontario and McMaster University Osteoarthritis Index (WOMAC)¹³. We will ask participants to record baseline and weekly WOMAC pain and function, the number of minutes of meditation practice and frequency of use of cognitive reappraisal. To evaluate changes in psychological functioning, we will administer a brief battery of self-report questionnaires that measure state emotion, emotion regulation, mindfulness skills, compassion, and pain catastrophizing before the intervention, midway and after the final week. For oxylipin and steroid profiling, usually 84 markers are positively detected and quantified even in healthy subjects using 150 ul plasma or serum. We expect higher concentrations of these markers in elderly subjects with OA pain. We expect differences in concentrations of these markers for MBSR or HEP groups.

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Methodology, selection criteria and recruitment: We will recruit 30 adults 50-80 years of age with symptomatic knee OA defined as pain in the index joint on most days of the past month, and radiographically confirmed OA structural lesions (Kellgren/Lawrence grade ≥ 2); we expect to have 20% dropout, leaving 24 participants completing the study. We will exclude participants using antipsychotic medications, who have alcohol or drug dependency, are scheduled to have joint replacement surgery in either leg within the next six months, or have inflammatory arthritis or avascular necrosis. The Clinical Trials arm of our Center for Musculoskeletal Health has successfully participated in and recruited numerous knee OA-related trials over a decade, and we are confident we will be able to achieve our goal.

Data Analysis Approach: Given that the proposed study is a feasibility study with very small numbers of participants, we will likely not reach significance for the pain outcomes; however, intention to treat (ITT) analysis will be undertaken to evaluate the effect of MBSR vs. HEP or vs. online MBSR. First we will compare the baseline characteristics using χ^2 test for categorical or nominal variables and t-test for continuous variables between MBSR and HEP groups. Second, we will assess whether, compared to HEP, MBSR results in significantly greater improvement in WOMAC pain or daily function, as well as for steroid and inflammatory markers. Using mixed models, we will compare the effect of MBSR vs. HEP on changes in WOMAC pain at each weekly visit from baseline using a mixed-effects regression model. Oxylipin and steroid profiles will be assessed by FDR-corrected univariate statistics in addition to partial least square regression analyses for differences in metabolites that are associated with pain change, in addition to correlation analysis of metabolic changes along the different time points of blood withdrawals.

4) Inclusion and Exclusion Criteria

We will be enrolling 30 subjects who have symptomatic knee osteoarthritis.

a) Inclusion Criteria

- Male or female, aged 50-80 years
- Positive “Frequent Knee Pain” question
- Radiographically confirmed knee OA (Kellgren/Lawrence ≥ 2)

b) Exclusion criteria

- Scheduled to have knee replacement surgery within 6 months from enrollment
- Rheumatoid arthritis or another inflammatory arthritis
- Known avascular necrosis
- Failure to comply with run-in procedures: poor attendance or non-compliant with completing the activity
- Major psychiatric illness, cognitive impairment or alcohol/substance abuse
- Non-English speaking

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Participants will be recruited by referral from their physician and posted announcements in the Department of Orthopedics Clinics, UC Davis Orthopaedic Surgery clinics, UC Davis Rheumatology Clinics, UC Davis primary care clinics, and local Sacramento and Davis senior community.

We will exclude the following special populations: adults unable to consent, individuals who are not yet adults, pregnant women, prisoners, and any UC Davis staff directly under the oversight of the Principle Investigators.

5) Study Timelines

The duration of an individual subject's participation in the study will be at least 10 weeks starting from the screening visit all the way to the follow-up visit.

The in-person MBSR course consists of 8 weekly classes plus 1 all-day class between Weeks 6 and 7, and is sequential. Depending on when a participant is consented, they may have to wait until a new 8-week course is available in order to begin. The HEP course also consists of 8 weekly classes and will start when a group of 7-10 participants have been assigned to the HEP intervention. The online MBSR course is designed to last 8 weeks and can be started at any time.

Since initiation of the in-person MBSR or HEP courses will depend upon when subjects are enrolled, it is not possible to provide the maximum length of time for a subject's participation. However long the subject's participation, they are only expected to complete 2 in-clinic visits and 8 weeks of class (plus 1 all-day class for MBSR).

Visits to the clinic may last from 1 to 2 hours. Weekly classes are 2.5 hours with the one-day retreat lasting from 10am to 5pm on a weekend day. The online MBSR course is roughly 20 minutes per day for 6-7 days of the week for 8 weeks.

We expect enrollment to occur over the course of 6 months. Final data collection is anticipated at 15 months.

6) Study Endpoints

Anticipated results, interpretation and pitfalls: We anticipate success in the feasibility Aim, and also that, compared with HEP, MBSR will result in greater improvement in pain and function in persons with knee OA. If this test study finds a positive feasibility result, we intend to proceed with a formal NIH clinical trial to establish the basis for introduction of MBSR practice into the standard armamentarium of knee OA treatment, as a primary or adjunct treatment. A negative result would also be important. If we have problems recruiting or bringing participants through the intervention, it will allow us to refine our approaches. Finally, a completely negative result with regard to pain and function here would have a critically important impact as well. MBSR is gaining significant attention in medicine as a potentially valuable clinical and research tool for pain and other conditions. If we find no association with important clinical outcomes in the fastest

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growing major painful health condition (OA), it would necessarily begin a critical discussion regarding the value of MBSR in the treatment of knee OA, as well as in other pain conditions.

7) Procedures Involved

The study will consist of two in-person clinic visits and the 8-week MBSR or HEP course.

Visit 1: Screening/Baseline (Clinic)

The following procedures will be performed:

1. Informed consent
2. Demographics (including age, sex, race, religious affiliation)
3. Tobacco smoking status
4. Vital signs (heart rate)
5. Height, weight, BMI
6. Medical/surgical history including history of pregnancies if applicable
7. Concomitant medication review
8. Inclusion/exclusion review
9. Blood draw (about 1.5 ml for oxylipin, cortisol, and other metabolite analyses with any leftover specimens banked for future use, 3 ml for CRP and 3 ml for ESR)
10. Saliva collection (about 1ml for cortisol analysis with the any leftover specimens banked for future use)
11. Surveys: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Emotion Regulation Questionnaire (ERQ), Five Facet Mindfulness Questionnaire (FFMQ), Pain Catastrophizing Scale (PCS)

Weeks 1 through 8 (MBSR or HEP course)

After the participant is verified as eligible to be enrolled and as completed all pre-treatment (i.e., baseline) assessments, they will be assigned to either the in-person MBSR course, the online MBSR course or the in-person group HEP course.

MBSR & HEP Courses

The weekly in-person HEP courses will be held at UC Davis Medical Center in Sacramento. The in-person MBSR courses have three locations: UCDMC, Sutter Health University in Sacramento, and Davis Holistic Health Center in Davis. Weekly classes will consist of didactic content, guided experiential meditation exercises, and group discussion. Additionally, the MBSR course will have an all-day class on a weekend day to be completed between Weeks 6 and 7.

The online MBSR course can be accessed at home or any place of the subject's choosing and will also consist of training in mindfulness meditation and mindfulness exercises. Training takes place twice per day, 10 minutes per session.

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Participants will complete self-reported online surveys (WOMAC) , weekly during treatment and at 2-week follow-up. ERQ will be completed once during the midpoint (around Week 5).

Visit 2: 2-Week Follow-Up (Clinic)

Within 2 weeks of the final class, subjects will return to clinic to complete the following:

1. Vitals (heart rate)
2. Blood draw (same as Visit 1)
3. Saliva collection (same as Visit 1)
4. Surveys (same as Visit 1)

All courses will be provided to enrolled subjects free of charge.

Schedule of Events

	Visit 1: Screening/ Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Visit 2: 2-Week Follow-Up
Informed Consent	X									
Inc/Exc Review	X									
Vitals X										X
Medical/Surgical History	X									
Concomitant Medication	X									
Demographics X										
Blood Draw	X									X
Saliva Collection	X									X
WOMAC X		X	X	X	X	X	X	XX		X
ERQ X						X				X
FFMQ X										X
PCS	X									X
Courses Below Will Be Assigned by Study Investigator										
In-Person MBSR Class		X X X	X X				X ^a X		X	
Online MBSR Class		X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	X ^b	
In-Person HEP Class		X X X	X X X X X							

^aSubjects assigned to the in-person MBSR course will also complete an all-day class on a weekend day between Weeks 6 and 7

^bSubjects assigned to the online MBSR course will complete self-directed classes at home

8) Data and/or Specimen Management and Confidentiality

We will implement a mixed model to examine the effect of treatment (MBSR vs online MBSR vs HEP) on changes in pain and psychological functioning from pre, weekly during treatment, post-treatment to 2-week follow-up. Because this is a pilot study with only 30 patients, there is no need for a power analysis. Each participant will be given a unique identification number that will be linked to all data collected. Names will not be used. This will provide confidential responses. Self-report data will be stored in password protected and encrypted spreadsheets. Blood samples will be stored in sub-zero freezers at the Center for Musculoskeletal Disorders at UC Davis medical Center in locked research labs and linked only to identification numbers (no names). All data will be stored for at least 7 years. All research personnel will complete HIPAA and confidentiality training.

9) Data and/or Specimen Banking

Left over blood or saliva samples will be banked for future use. At the end of the study, the key that links the samples to the subjects will be destroyed. All samples will be stored without identifiers. As this is a pilot study, we may develop novel ideas in the future as it relates to this study and may want to conduct additional analyses. The samples will be stored indefinitely in a controlled-accessed location. We do not intend to share these samples outside of the research group.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

There will be continuous safety surveillance with emphasis on the potential side effects of each intervention, as detailed below. Participation in the study will be discontinued if the subject fails to adhere to the study requirements in a way that may cause harm to him or herself or seriously interfere with the validity of the study results; or the investigator determines that further participation would be detrimental to the subject's health or well-being. Subjects who are injured as a result of being in this study will have treatment available. The costs of such treatments may be covered by the University of California depending on a number of factors.

Data and Safety Monitoring Plan (DSMP): The Data and Safety Monitoring Plan for the proposed project incorporates the policies on human subject data and safety monitoring specified by the UC Davis IRB. Since this is not a NIH-defined Phase III Clinical Trial and it is a low risk trial at a single site, a formal Internal and External Review Board is not required, and the PI can conduct the data and safety monitoring in conjunction with the UC Davis IRB. The PI of the project along with relevant project staff will meet regularly with the Clinical Coordinator/Data Manager (post-doctoral fellow) to review issues of data quality or other issues that might arise. The PI will be responsible for evaluating any adverse event and if necessary reporting it to the IRB.

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1. **Risk assessment – minimal risk:** This study represents a minimal risk to study participants since it is a behavioral intervention study and prior studies with mindfulness meditation (MBSR) have not demonstrated the occurrence of serious adverse events.
2. **Description of adverse event grading and anticipated adverse events:** An adverse event (AE) is here defined as any unfavorable and unintended sign, symptom, injury or disease temporarily associated with an intervention or procedure, regardless of whether it is considered related to an intervention or procedure that occurs during the course of the study. There is a minimal risk of an unfavorable psychological event, which has generally not been observed in other trials of MBSR. Therefore, the likelihood and seriousness of this risk is small.
3. **Description of monitoring study progress and safety of human subject participants:** The principal investigator, Barton L. Wise, MD, MSc, FACP, has primary responsibility for the overall conduct of the study and for the safety of participating human subjects. The PI will ensure that (1) the informed consent process is conducted appropriately and that informed consent is obtained prior to proceeding with any study procedures; (2) only eligible subjects, per protocol eligibility criteria, are enrolled in the study; (3) data are collected and analyzed per protocol requirements; (4) procedures are implemented to ensure that the project is consistently monitored for possible adverse events; (5) adverse events are reviewed promptly and reported as required to the IRB; (6) the privacy and confidentiality of study subjects is maintained. Monitoring for adverse events will occur in real time at the single site, and the PI will be made aware of potential adverse events immediately during the conduct of the trial by study staff. When an event occurs, the PI will make an estimation of whether it is serious or likely to be related to the study interventions; serious adverse events or reportable new information will be reported to the IRB following local guidelines. If events are minor or unrelated, they will be collected and reviewed on a yearly basis to examine for unforeseen patterns. While implementation of aspects of the DSMP may be delegated to members of the research team, the PI maintains ultimate responsibility for the project and for the safety of study participants. The PI, Dr. Wise, has served in the past as designated safety officer for multiple NIH/NIAMS sponsored clinical trials, and thus has significant experience with the process and with consideration of potential adverse events.

11) **Withdrawal of Subjects**

The study doctor or the IRB can remove subject from the research study without their approval. The study doctor may stop subjects' participation in the study at any time for any reason if, in his/her judgment, continuation of study is not in the subject's best interest. Possible reasons for stopping study participation may include:

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- Subject does not meet study requirements
- Subject does not follow the study instructions given by the study doctor or study staff;
- Subject does not show up for scheduled visits;
- The study doctor determines that it is not in the best interest of the subject to continue in the study;
- Administrative reasons

12) Risks to Subjects

Possible risks/inconveniences to subjects include:

1. Venipuncture: Pain, bruising, or infection at the site of blood draw.
2. Loss of confidentiality: Participation in research can involve loss of privacy. Research records will be kept confidential to the extent permitted by law. Subjects will be identified by a code, and personal information from records will not be released without written permission. Subjects will not be personally identified in any publication about the study.
3. Mindfulness-Based Stress Reduction Training (MBSR): There is minimal risk associated with participating in the MBSR intervention. If we or our contracted trainer observes any evidence of significant depression we will refer the participant to psychological services.
4. Health Enhancement Program (HEP): There is minimal risk associated with participation in the HEP alternate intervention. The only potential risks are the same as attending a series of sit down lectures. If we observe any unusual or unforeseen behavior, we will refer the participant to psychological services.

13) Potential Benefits to Subjects

There is no guaranteed benefit to subjects who participate in this study. The benefits of participation in this study include social participation in a group activity and the opportunity to contribute to scientific understanding that may lead to treatment for an unmet health need. The information gathered in this study will be very important in learning whether targeted MBSR can improve pain or function in osteoarthritis. Improvement in pain or function could promote health and improved social participation in older adults.

14) Multi-Site Research

N/A

15) Community-Based Participatory Research

N/A

16) Sharing of Results with Subjects

Research results for each individual participant will not be shared.

17) Prior Approvals

N/A

18) Provisions to Protect the Privacy Interests of Subjects

Subject’s personal and medical information will be kept confidential. Each subject will be given a subject identification number that will be used throughout the study on any source documents, blood samples or other study materials. In addition to signing a consent form subjects will also be signing a HIPAA release form, which allows the study team to access subject UCD medical records for research purposes only. On the HIPAA form subjects can select what parts of their medical history they are giving us permission to access.

During the consent process subjects will be provided with an explanation regarding how we plan on protecting their privacy by keeping their personal and medical records confidential.

Only trained study staff will have access to study records, which will be stored in a locked cabinet in a secure building.

19) Compensation for Research-Related Injury

Subjects will be provided with contact information and asked to promptly report any injury believed to be related to their participation in this study. If a subject is injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or may be billed to the subject’s insurance company just like other medical costs. The University does not normally provide any other form of compensation for injury.

20) Economic Burden to Subjects

The investigator is paying for all study procedures and subjects will receive compensation for participating in the study; therefore there will not be any costs that the subjects will be responsible for related to their participation in this study.

21) Drugs or Devices

Not applicable.

22) [ClinicalTrials.gov](https://clinicaltrials.gov) Registration

This study will be registered with [ClinicalTrials.gov](https://clinicaltrials.gov).

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on [Clinicaltrials.gov](https://clinicaltrials.gov).

Yes	
<input type="checkbox"/>	This study is funded by the NIH . (If this study is not funded by NIH, go to Section 2.)
<input checked="" type="checkbox"/>	One or more human subjects will be prospectively assigned to one or more

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	interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
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Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
<input type="checkbox"/>	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
<input type="checkbox"/>	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.
<input type="checkbox"/>	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click [here](#).

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
<input checked="" type="checkbox"/>	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention <i>and</i> a health outcome.
<input checked="" type="checkbox"/>	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations .

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
<input type="checkbox"/>	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

23) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
<input checked="" type="checkbox"/>	This research involves no more than minimal risk.
<input checked="" type="checkbox"/>	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
<input checked="" type="checkbox"/>	This research is not subject to FDA jurisdiction.

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<input checked="" type="checkbox"/>	This research does not include prisoners as participants.
<input checked="" type="checkbox"/>	This research is not part of an IRB reliance.
<input checked="" type="checkbox"/>	This research is not subject to SCRO oversight.
<input checked="" type="checkbox"/>	This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).
<input checked="" type="checkbox"/>	This research does not involve personnel supported by federal training, center, or program grants.
<input checked="" type="checkbox"/>	No personnel involved in the design, conduct, or reporting of this research have a financial interest (RFI) in this study.

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