Evidence-based Practice Center Systematic Review Protocol

Project Title: Meditation Programs for Stress and Well-Being

Amendment Date(s) if applicable: October 10, 2012

(Amendments Details–see Section VII)

I. Background

Meditation is used widely by both clinical populations and the general public to treat stress and stress-related conditions, as well as to promote health.[1, 2] A number of hospitals and programs offer courses in meditation to patients seeking alternative or additional methods to relieve ailments, or to promote health. Given the increasing use of meditation across a large number of conditions, examining the effects of meditation, type of meditation, conditions for which they are efficacious, and any mechanisms of action are important for patients, clinicians, and policy makers.

There remains uncertainty about the differences and similarities between the effects of different forms of meditation. Some have challenged "mindfulness" as a useful umbrella term for the practice, since it is understood and practiced in different ways.[3, 4] Some "mindfulness" approaches such as Dialectical Behavioral Therapy (DBT) and Acceptance and Commitment Therapy (ACT) do not use mindfulness as the foundation but rather as an ancillary component. Others, such as Yoga and Tai Chi, involve a significant amount of movement which could produce their own physiological effects apart from the mental exercises, potentially confounding any association between the mental activities of meditation and outcomes. Most of the other meditative programs involve a stilling of the mind in some form to increase awareness, and then involve some further mental activity with that awareness that may have considerable overlap in practice. Academically, these programs have been described as "concentrative" meditation, such as Transcendental Meditation (TM), or "mindfulness" meditation such as MBSR (Mindfulness Based Stress Reduction); however this distinction may not differentiate the effects of the techniques.[3] The effectiveness of these interventions is unclear and may vary among different subgroups such as those with a particular clinical condition (e.g. anxiety or pain). This review will determine whether the effects of various meditation programs on various stress outcomes are similar or different.

The effects of the movement-based meditative techniques such as Yoga, Tai chi, and Qi gong on stress outcomes are influenced by the ancillary beneficial effects of exercise/movement components on stress outcomes. Although these techniques also contain a meditative component, it is often difficult to ascertain the effects of meditation itself on stress outcomes, separate from the effects of exercise component.[25,26] Many of the Yoga interventions, in particular, do not clearly indicate how much meditation is involved in the intervention, leaving concerns that the inclusion of these studies will potentially confound conclusions about the effects of meditation. Like Yoga, Qi gong is a broad term encompassing both meditation and movement, and comes with some of the same difficulties as Yoga in terms of parsing the effects of movement from the effects of meditation. Due to issues of scope, and to ensure consistency with the nomination, our review will largely focus on those meditative programs that are more purely meditative.

Meditation programs are varied and can be defined in a number of ways. In order to evaluate programs that are more than a brief mental exercise, yet remain broadly inclusive, we define a meditation program as any systematic or protocolized meditation program that follows a predetermined curriculum. We define these programs to involve, at a minimum, at least four hours of training with instructions to practice outside the training session.

While both clinical and healthy populations use meditation, this report seeks to assess the impact of the meditation programs on clinical populations. Although meditation is used by many as a way to promote

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health, the relevance of meditation programs for those with a disease or condition is more pressing for payors, clinicians, and patients. Since meditation is thought to have its effects by reducing the role of stress in the etiology of disease, we will include any population identified with a particular stressor as part of the spectrum of clinical conditions. The review will evaluate the effect of meditation programs on a range of important outcomes related to stress and well-being.[5] The selected outcomes fall into domains based on the Patient Reported Outcomes Measurement Information System (PROMIS) framework: negative affect, positive affect, well-being, cognition, and health-related behaviors affected by stress such as substance abuse, sleep and eating behaviour.[5] The review will also evaluate the effect of meditation programs on the clinical outcomes of pain and weight.

Previous Systematic Reviews on this topic

A number of previous reviews have been conducted.[6-20] However, these have been largely limited to one form of meditation or another (e.g. Mindfulness Based Stress Reduction) usually with a narrow clinical focus on a limited range of outcomes.[6-21] These studies have demonstrated that meditation has an effect in largely uncontrolled or wait-list controlled studies. However, it is unclear whether these effects are specific to meditation, and whether these effects are seen in higher quality trials with appropriate comparators.[22,23] A number of factors such as attention and expectancy of benefit can affect trial results from such studies. In a situation where double blinding may not be feasible, the burden of the design issues is higher to control for these types of effects.[25]

Behavioral trials are susceptible to biases that may not be seen in pharmaceutical trials. However, prior reviews have tended to assess behavioral trials with the same bias measures used for pharmaceutical trials. They have underemphasized measures that are important for behavioral trials (e.g. controlling for expectancy), and have inadequately evaluated these expectancy effects as well as other risk of bias measures such as the blinding of outcome assessors.[25, 26]While some reviews have focused on randomized controlled trials, many if not most of the included studies involved wait list or usual care controls. Additionally, previous reviews have overemphasized certain bias measures such as blinding of the intervention in the Jadad scale which are more appropriate for pharmaceutical interventions and not possible in meditative studies. . Furthermore, given the anticipated large number of trials that have moved to a more rigorous design standard of using higher quality controls in recent years, a systematic review of such trials on the outcomes of stress with appropriate control for these design effects is potentially useful to decision-makers and stakeholders. Hence, this systematic review will evaluate the effect of meditative programs on affect, attention, health related behaviors affected by stress, pain, and weight, among those with a medical or psychiatric condition in randomized controlled trials.

Expected Use of the Report

A rigorous systematic review of meditation in addressing the effects on positive and negative affect, attention, well-being, health-related behaviors affected by stress, pain, and weight may be potentially useful to patients, clinicians, and policy-makers. The results of the proposed review will likely be useful for clinicians and patients in making decisions about the best available options for stress reduction among these populations. The results of the proposed review will also inform developers of professional guidelines for these conditions. This review will also identify those areas in which there are inadequate evidence to inform the design of future studies in these areas.

II. The Key Questions

KQ 1:	**What are the efficacy and harms of Meditation Programs on negative affect (e.g. anxiety, stress) and positive affect (e.g. well being) among those with a clinical condition (medical or psychiatric)?**
KQ 2:	**What are the efficacy and harms of Meditation Programs on attention among those with a clinical condition (medical or psychiatric)?**
KQ 3:	**What are the efficacy and harms of Meditation Programs on health-related behaviors affected by stress, specifically substance use, sleep, and eating, among those with a clinical condition (medical or psychiatric)?**
KQ4:	**What are the efficacy and harms of Meditation Programs on pain and weight among those with a clinical condition (medical or psychiatric)?**

Summary of revisions to key questions

As a result of public comment and TEP input, we have added a KQ on the clinical outcomes of pain and weight among those with a clinical condition.

To limit the scope of the review we will only evaluate meditative programs that are purely meditative, consistent with the original nomination. Thus, movement based meditation programs will not be evaluated. Due to the need to limit scope, we have also focused on clinical populations.

We have replaced the KQ on physical function as it would primarily apply to the movement-based meditation programs and will not be addressed in this review. The movement-based programs require their own nomination and evaluation in a separate systematic review given the large number of randomized trials for these interventions.

We have refined KQ2 to evaluate the effects on attention as this is a key outcome for understanding mechanisms. With respect to KQ3, we have re-added evaluation of eating behavior on the recommendations of the TEP panel, since it appears to be heavily influenced by stress. Eating behavior will be measured by food diaries. However, since weight is affected by multiple inputs including eating, weight will be evaluated as its own clinical outcome in KQ4, along with pain.

On TEP input we have removed the question on surrogate outcomes and focused on clinical outcomes of pain and weight that are of higher priority. Based on TEP input we have removed the question about the time-course and pattern of changes because of the lack of clarity and specificity in the original question

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Table 1: PICOTS for each Key Question

	KQ1: Negative and positive affect	KQ2: Attention	KQ3: Health-related behaviors affected by stress	KQ4: Pain & weight
Population(s)	Medical or psychiatric	Medical or psychiatric	Medical or psychiatric	Medical or psychiatric
Interventions	Mindfulness meditation (Vipassana, Zen, MBSR, MBCT, other mindfulness), Mantra meditation (TM, other mantra based), Meditative prayer, Sahaj yoga, Dhyan yoga	Mindfulness meditation (Vipassana, Zen, MBSR, MBCT, other mindfulness), Mantra meditation (TM, other mantra based), Meditative prayer, Sahaj yoga, Dhyan yoga	Mindfulness meditation (Vipassana, Zen, MBSR, MBCT, other mindfulness), Mantra meditation (TM, other mantra based), Meditative prayer, Sahaj yoga, Dhyan yoga	Mindfulness meditation (Vipassana, Zen, MBSR, MBCT, other mindfulness), Mantra meditation (TM, other mantra based), Meditative prayer, Sahaj yoga, Dhyan yoga
Comparators	Active Attention Education	Active Attention Education	Active Attention Education	Active Attention Education
Outcome measures	1. Self-reports of negative (including perceived stress) and positive affect. 2. Clinician reports of negative affect	1. Experimental measures of attention	1. Self- reports of substance use (cigarettes, alcohol, illicit substances), sleep, and eating 2. Clinician reports of substance abuse, sleep and eating disorders	1. Self-reports of pain intensity and interference 2. Clinician measures of weight, body mass index
Timings	Longitudinal	Longitudinal	Longitudinal	Longitudinal
Settings	Clinical settings	Clinical settings	General and clinical settings	Clinical settings
Adverse effects of intervention, treatment burden	Any	Any	Any	Any

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III. Figure 1. Analytic Framework

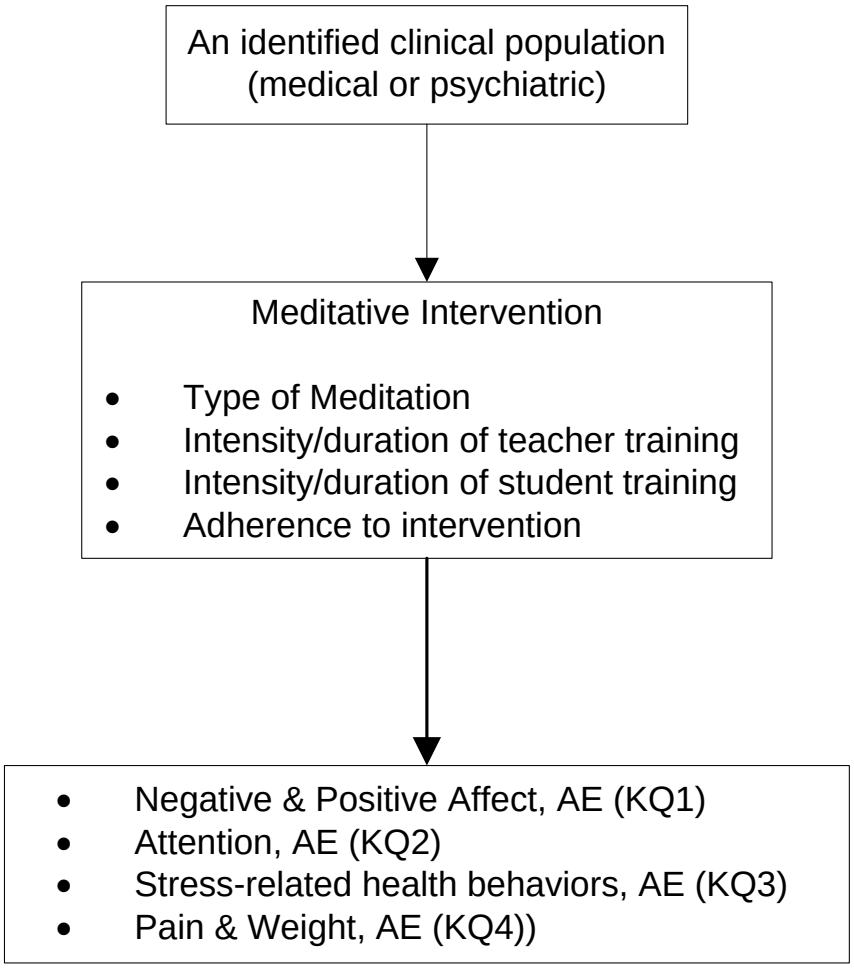

Figure 1: This figure depicts the key questions within the context of the PICOTS described in the previous section. Adverse events (AE) may occur at any point after the meditation program.

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IV. Methods

A. Table 2. Criteria for Inclusion/Exclusion of Studies in the Review

	Inclusion	Exclusion
Population and condition of interest	Adult populations (18 yrs or older) that have a clinical (medical or psychiatric) diagnosis including pregnancy and post-partum period. As long as prison populations are identified with a clinical condition,(medical and psychiatric) they will be included.	Studies of children and healthy individuals. The type & nature of meditation taught to children would be significantly different from adults.
Interventions	We will include any structured meditation programs (any systematic or protocolized meditation programs that follow predetermined curricula). We define these programs to involve, at a minimum, at least 4 hours of training with instructions to practice outside the training session. These include: • MBSR • MBCT • TM • Vipassana • Zen • Meditative prayer • Sahaj yoga • Dhyan yoga • Other mindfulness meditation • Other mantra meditation	Any meditation programs in which the meditation is not the foundation and majority of the intervention. These include: • Dialectical Behavioral Therapy (DBT) • Acceptance and Commitment Therapy (ACT). • Any of the movement- based meditations such as Yoga, Tai chi, and Qi gong • Chi kung • General yogas (e.g. Iyengar, Hatha) • Shavasana • Aromatherapy • Biofeedback • Neurofeedback • Hypnosis • Autogenic training • Psychotherapy • Laughter therapy • Therapeutic touch • Eye movement desensitization reprocessing • Relaxation therapy • Spiritual therapy • Breathing exercise • Exercise • Pranayama Any intervention that is given remotely, or only by video or audio to an individual without the involvement of a meditation teacher physically present
Comparisons of interest	Studies that compare the intervention to either an attention, active or education control. Active controls could include other meditation programs, pharmacotherapy or other	Any studies that only evaluate a wait-list / usual care control or do not include a comparison group

	interventions.	
Outcomes	1. Affect a. Negative i. Anxiety ii. Depression iii. Perceived Stress b. Positive i. Subjective well being 2. Cognition and neuropsychological function a. Attention (Stroop, continuous performance as measure of attention, others) 3. Health-related behaviors affected by stress a. Substance use i. Alcohol abuse ii. Smoking/tobacco abuse iii. illicit drugs use b. Sleep c. Eating (food diaries) 4. Clinical outcomes a. Pain (intensity and interference) b. Weight (BMI and weight loss) 5. Harms (any noted by the study such as exacerbation of psychosis)	
Type of study	Randomized controlled trials.*	• Articles with no original data (reviews, editorials, comments). • Studies published in abstract form only • Dissertations • Non randomized designs
Timing and Setting	We will include studies that occur in general and clinical settings, and are longitudinal.	

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*Randomized designs that involve either an active control, attention control, or education control that reliably controls for "placebo effects" such as expectation of benefit and attention provide the best evidence of whether an intervention shows efficacy due to the intervention as opposed to efficacy due to a nonspecific placebo type effect. They also minimize the effects of selection bias and confounding.[22-24,27] We will prioritize evidence strategies regarding study designs for relevant key questions using a transparent framework.[28] We will determine what other study designs other than RCTs will be informative on harms of these meditative techniques and may consider lowering our evidence threshold to identify relevant harms. Any subsequent modifications to the inclusion/exclusion of study designs will depend on the availability of studies on that Key Question and will be noted as a protocol amendment.

B. Search Strategy

We will search the following databases for primary studies: MEDLINE®, PsycINFO, EMBASE®, PsycArticles, SCOPUS, CINAHL, and the Cochrane Library. We will develop a search strategy for MEDLINE, accessed via PubMed, based on an analysis of the medical subject headings (MeSH) terms and text words of key articles identified a priori. The search will be updated during the peer review process. The search strategy for MEDLINE can be found in **Appendix A.** We will also review the reference lists of each included article, relevant review articles and related systematic reviews. We will also use prior systematic reviews to identify studies. We plan to evaluate non-English studies, and will update the search during the peer review process.

C. Data Abstraction and Data Management

We will use DistillerSR (Evidence Partners, 2010), to manage the screening and review process. DistillerSR is a web-based database management program that manages all levels of the review process. All applicable citations identified by the search strategies are uploaded to the system.
Two independent reviewers will conduct title scans. For a title to be eliminated at this level, both reviewers will need to indicate that the study was ineligible. If the reviewers disagree, the article will be advanced to the next level, abstract review.

Abstracts will be reviewed independently by two investigators, and will be excluded if both investigators agree that the article meets one or more of the exclusion criteria (see inclusion and exclusion criteria listed in Table 2). Differences between investigators regarding abstract inclusion or exclusion will be tracked and resolved through consensus adjudication. Articles promoted on the basis of abstract review will undergo another independent parallel review to determine if they should be included in the final qualitative and quantitative systematic review and meta-analysis. The differences regarding article inclusion will be tracked and resolved through consensus adjudication. We will maintain a list of excluded articles and the potential reasons for exclusion.

We will use a systematic approach for extracting data to minimize the risk of bias in this process. We will create standardized forms for data extraction, which will be pilot tested. By creating standardized forms for data extraction, we will maximize consistency in identifying all pertinent data available for synthesis. Each article will undergo double review by study investigators for data abstraction. The second reviewer will confirm the first reviewer's data abstraction for completeness and accuracy. Reviewer pairs will be formed to include personnel with both clinical and methodological expertise. A third reviewer will audit a random sample of articles by the first two reviewers to ensure consistency in the data abstraction of the articles. Reviewers will not be masked to the articles' authors, institution, or journal. For all articles, reviewers will extract information on general study characteristics (e.g., study design, study period, and follow-up), study participants (e.g., age, gender, race, comorbidities,), eligibility criteria, interventions, outcome measures and the method of ascertainment, and the results of each outcome, including measures of variability.

For each meditation program we will extract information on measures of intervention fidelity including dose, training and receipt of intervention by measuring 1) duration of structured training in meditation for

the participants 2) mean hours of total meditation (training + home) 3) hours/duration of recommended practice 4) description of participant compliance if any 5) description of participant proficiency in practicing the meditation technique 6) description of instructor qualifications.

All information from the article review process will be entered into the DistillerSR database by the individual completing the review. Reviewers will enter comments into the system whenever applicable. The DistillerSR database will be used to maintain the data, as well as to create detailed evidence tables and summary tables.

D. Assessment of Risk of Bias of Individual Studies

The risk of bias of included trials will be conducted independently and in duplicate based on the recommendations in the Guide for Conducting Comparative Effectiveness Reviews [29] We will supplement these tools with additional assessment questions based on the Cochrane Collaboration's Risk of Bias Tool.[30, 31] The selected risk of bias items are outlined below. For example, while double blinding may not be possible in meditation studies, we will evaluate blinding of data collection personnel, especially with subjective outcomes. In addition we will assess whether the attention control was matched on expectation, time, and attention. One individual will extract information, and a second senior reviewer will verify the information. A third reviewer will resolve discrepancies

Selection Bias:

- Was the method of randomization described in the paper, and was it appropriate (random number generator or table; allocation concealment)?
- Did the strategy for recruiting participants into the study differ across study groups?

Performance Bias:

- Was the control matched for time and attention by the instructors (100%, 75%, ≤50%)
- Was an assessment for credibility of the control used?
- Was it adequate (e.g. would you recommend this to your friends?)?

Attrition Bias:

- Was there a description of withdrawals and dropouts? If so, was there a high rate of attrition of differential or overall attrition?
- Did attrition result in a difference in group characteristics between baseline and followup?
- Was intent-to-treat analysis used?

Detection Bias:

- Were those who collected data on the participants blind to the allocation?
- Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
- Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
- Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?

Reporting Bias:

- Are the potential outcomes prespecified by researchers?
- Are all prespecified outcomes reported?

The overall risk of bias will be assessed as:

- **Good (low risk of bias).** These studies had the least bias, and the results were considered valid. These studies adhered to a clear description of the population, setting, approaches, and

comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; a low dropout rate; and clear reporting of dropouts.

- **Fair.** These studies were susceptible to some bias, but not enough to invalidate the results. They did not meet all the criteria required for a rating of fair because they had some deficiencies, but no flaw was likely to cause major bias. The study may have been missing information, making it difficult to assess limitations and potential problems.

- **Poor (high risk of bias).** These studies had significant flaws that might have invalidated the results. They had serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

E. Data Synthesis

For each Key Question, we will create a set of detailed evidence tables containing all information abstracted from eligible studies. We will conduct meta-analyses when there is sufficient data (at least 3 studies that sufficiently homogenous with respect to the population characteristics and study duration, and meditation "dose"). We will conduct narrative synthesis when study results cannot be combined.

For studies amenable to pooling with meta-analyses, we will calculate pooled mean differences, risk differences or relative risks using a DerSimonian and Laird random effects model. For studies with continous outcomes we will only combine studies using mean differences if multiple trial reports use the same or similar scales. Standardized mean difference (SMD) will be used when the same outcome (such as anxiety or depression) is measured using different scales. SMD is the mean difference divided by a measure of within group standard deviation. Effect sizes will be estimated in Standard deviation units. Either using Cohen's *d* or Hegde's *g* for all studies that provide sufficient data.[32]

We will identify statistical heterogeneity between the trials in all the meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10, and (2) an I-squared statistic with a value greater than 50% indicating substantial heterogeneity. We will not report the pooled result if substantial heterogeneity is found. We will conduct sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we will conduct formal tests for publication bias using Begg's and Eggers tests including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses will be conducted using STATA (Intercooled, version 11, StataCorp, College Station, TX) or Stats Direct.

When we are unable to pool studies, we will calculate and display the individual mean differences, risk differences or relative risks with 95% confidence intervals (CI) for the individual studies. We will model rare adverse events (<1%) using the Peto Odds ratio approach which has the best confidence interval coverage for rare events, because the random effects model is statistically underpowered.[33] If we detect an imbalance in trial sizes and number of zero event studies, appropriate sensitivity analysis using treatment arm continuity correction approaches will be conducted. [34]

F. Grading the Evidence for Each Key Question

At the completion of our review, we will grade the quantity, quality and consistency of the best available evidence addressing Key Questions 1 – 6 by adapting an evidence grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.[29] In assigning evidence grades we will consider the domains of risk of bias of included studies, directness, consistency, and precision and publication bias. We will also consider additional domains such as biological plausibility, dose-response effect and, impact of plausible confounders when applicable. Evidence will be graded for the outcomes in the Key Questions.

We will classify evidence pertaining to Key Questions into four basic categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate); and (4) "insufficient" grade (evidence is unavailable).

G. Assessing Applicability

Applicability will be assessed separately for the different outcomes for the entire body of evidence guided by the PICOTS framework as recommended in the Methods Guide for Comparative Effectiveness Reviews of Interventions.[29] Potential factors to be assessed which may limit applicability include intervention fidelity such as duration of structured meditation training, total amount of meditation practice (dose of meditation), subject compliance with meditation, subject proficiency with meditation, instructor qualifications, and study selection criteria for participants. There are concerns that participants in meditation studies are highly selected, such as trained meditators. We will evaluate the selection process of these studies to determine such issues around applicability. We will also examine whether race or ethnicity or education modifies the effect of meditation,

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VI. Definition of Terms

MBSR = Mindfulness Based Stress Reduction
MBCT= Mindfulness Based Cognitive Therapy
TM = Transcendental Meditation
ACT = Acceptance and Commitment Therapy

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DBT = Dialectical Behavioral Therapy
RCT = Randomized controlled trial

VII. Summary of Protocol Amendments

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Protocol Amendments on October 10, 2012

Date	Section	Original Protocol	Revised Protocol	Rationale
October 10th, 2012	Analytical Framework	Fig 1. Analytic Framework The original AF describes a clinical population that undergoes a meditative intervention that is characterized by dose, intensity, and teacher qualifications. The outcomes follow from this box.	We revised the analytic framework to divide meditation interventions into two interventions: mindfulness and mantra. The analytic framework was revised to divide the trials into those whose comparator is a nonspecific active control or specific active control. Finally, the outcomes were updated in the figure to reflect the current organization of outcomes in more detail. The mental component of health-related quality of life was added as a separate bullet from positive and negative affect under KQ1.	We made these protocol amendments to provide a higher level of synthesis of the strength of evidence of the literature for these categories (mindfulness and mantra; nonspecific and specific active control) instead of grading the strength of evidence for numerous small bodies of evidence that in many cases would consist of only a single trial. A nonspecific active control only matches time and attention, and is not a known therapy. A specific active control compares the intervention to another known therapy, such as progressive muscle relaxation. The nonspecific active controls are similar and provide a consistent comparator for the trials when assessing the strength of evidence. However, there is significant heterogeneity in the specific active controls, and results from these trials are not easily comparable to those with a nonspecific active control The mental component of health related quality of life was originally lumped under the other mental health measures, but should be its own outcome. Although it shares some of the attributes of the other mental health outcomes (the reason it was categorized there originally), we realized it is distinct from positive and negative affect.

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Date	Section	Original Protocol	Revised Protocol	Rationale
October 10th, 2012	F. Grading the Evidence for Each Key Question	**F. Grading the Evidence for Each Key Question** At the completion of our review, we will grade the quantity, quality and consistency of the best available evidence addressing Key Questions 1 – 6 by adapting an evidence grading scheme recommended by the Methods Guide for Conducting Comparative Effectiveness Reviews.[29] In assigning evidence grades we will consider the domains of risk of bias of included studies, directness, consistency, and precision and publication bias. We will also consider additional domains such as biological plausibility, dose-response effect and, impact of plausible confounders when applicable. Evidence will be graded for the outcomes in the Key Questions. We will classify evidence pertaining to Key Questions into four basic categories: (1) "high" grade (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of the effect); (2) "moderate" grade (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of the effect and may change the estimate); (3) "low" grade (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of the effect	1) As part of the effort to synthesize a very heterogeneous body of evidence, we modified the plans to conduct difference in change calculation for each outcome. This is not a statistical analysis, but rather a way to visually display the data. This will be done by the following formula: {(meditation T2-T1)-(control T2-T1)}/(meditation T1) where T1 is the baseline mean score and T2 is the followup mean score. Since many trials do not provide enough information to calculate a confidence interval around the difference in change estimate, we will also conduct meta-analysis whenever possible to provide an estimate of the precision of reported effects. The resulting estimate of precision will be used in the final grading of the strength of evidence. The difference in change graphs will be used to determine the consistency of reported effects. 2) For the large bulk of outcomes, measures were rated as direct measures of that outcome. However, since anxiety, depression, and stress/distress are components of negative affect, we will rate them as indirect measures of negative affect. If a direct measure of negative affect is available, we will use that measure instead of any indirect measures. 3) To clarify our plans regarding the assessment of publication bias, we cannot conduct any reliable quantitative tests for publication bias since few studies are available for most outcomes, and we are unable to include all eligible studies in the meta-analysis due to missing data. Consequently, funnel plots are unlikely to provide much useful information regarding the possibility of publication bias. We will conduct a qualitative assessment of publication bias. We will review all the randomized trials of meditation listed in the clinicaltrials.gov	1) To provide more detail on how we will assess two of the domains of SOE -consistency and precision. Also to point out that we will provide two ways of viewing the data, one arithmetic way that incorporates baseline differences and the other a statistical analysis that does not adjust for baseline differences. 2) To point out that in the higher level synthesis of negative and positive affect, we will treat the component measures as indirect measures since they reflect a component of the outcome but there are more direct measures of those domains. 3) To specify the details of how we will grade the overall strength of evidence. We did not fomally consider publication bias in assigning the SOE, we described the results of our assessment of publication bias when applicable.

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		and is likely to change the estimate); and (4) "insufficient" grade (evidence is unavailable).	registry, and will search for any trials that completed recruitment 3 or more years ago that did not publish results, or listed outcomes for which they did not report results. To assess for selective outcomes reporting, we will examine the methods section of each study for all the scales used to measure outcomes and assess whether the studies reported results for all of them. To examine sponsorship biases, we will also evaluate the potential funding sources of these studies. We have prepared the following algorithm to clarify our approach to grading the strength of evidence. (Figure 2) (see below)	
October 10th, 2012	E. Data Synthesis	**E. Data Synthesis** For each Key Question, we will create a set of detailed evidence tables containing all information abstracted from eligible studies. We will conduct meta-analyses when there is sufficient data (at least 3 studies that sufficiently homogenous with respect to the population characteristics and study duration, and meditation "dose"). We will conduct narrative synthesis when study results cannot be combined. For studies amenable to pooling with meta-analyses, we will calculate pooled mean differences, risk differences or relative risks using a DerSimonian and Laird random effects model. For studies with continous outcomes we will only combine studies using mean differences if multiple trial reports use the same or similar scales. Standardized mean difference (SMD) will be used when the same outcome (such as anxiety or depression) is measured using different scales. SMD	As part of the effort to achieve a higher level of synthesis of the evidence, we will perform a hierarchical synthesis of the effects of interventions on negative affect. We will combine stress and distress into a single outcome, and also combine well-being and positive mood into a single outcome of positive affect. We will do this because of the paucity of studies reporting on these outcomes and the similarities between these outcomes. To analyze the effects of meditation programs on negative affect, we will combine one negative affect scale per trial with the others. Since some trials report on more than one negative affect scale, we will give first priority to anxiety, then depression, then stress/distress. Anxiety is a primary dimension of negative affect and a common symptom of stress. Anxiety is highly correlated with depressive symptoms, and is expected to be a good primary marker of negative affect in the samples included in these analyses when more than one measure of negative affect is available. We will also conduct a sensitivity analysis of this analysis by reversing the prioritization order such that stress/distress is prioritized over depression which is prioritized over anxiety	To respond to suggestions to provide a higher level of synthesis for end-users of this report

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		is the mean difference divided by a measure of within group standard deviation. Effect sizes will be estimated in Standard deviation units. Either using Cohen's *d* or Hegde's *g* for all studies that provide sufficient data.[32] We will identify statistical heterogeneity between the trials in all the meta-analyses using: (1) a chi-squared test with a significance level of alpha less than or equal to 0.10, and (2) an I-squared statistic with a value greater than 50% indicating substantial heterogeneity. We will not report the pooled result if substantial heterogeneity is found. We will conduct sensitivity analyses by omitting one study at a time to assess the influence of any single study on the pooled estimate. For all meta-analyses, we will conduct formal tests for publication bias using Begg's and Eggers tests including evaluation of the asymmetry of funnel plots for each comparison of interest. All meta-analyses will be conducted using STATA (Intercooled, version 11, StataCorp, College Station, TX) or Stats Direct. When we are unable to pool studies, we will calculate and display the individual mean differences, risk differences or relative risks with 95% confidence intervals (CI) for the individual studies. We will model rare adverse events (<1%) using the Peto Odds ratio approach which has the best confidence interval coverage for rare events, because the random		

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		effects model is statistically underpowered.[33] If we detect an imbalance in trial sizes and number of zero event studies, appropriate sensitivity analysis using treatment arm continuity correction approaches will be conducted.		
October 10th, 2012	Data Synthesis (Meta-analysis)	For all meta-analyses, we will conduct formal tests for publication bias using Begg's and Eggers tests including evaluation of the asymmetry of funnel plots for each comparison of interest.	Please see response #3 in the following section above: F. Grading the Evidence for Each Key Question Since publication bias is a grading issue, we have added text to the Grading the Evidence section in our response above	We cannot assess publication bias quantitatively due to the paucity of studies, and missing data that precludes inclusion of some studies in meta-analysis. Our revised plan takes this into account and provides a plan for qualitative assessment.

Figure 1. Analytic Framework

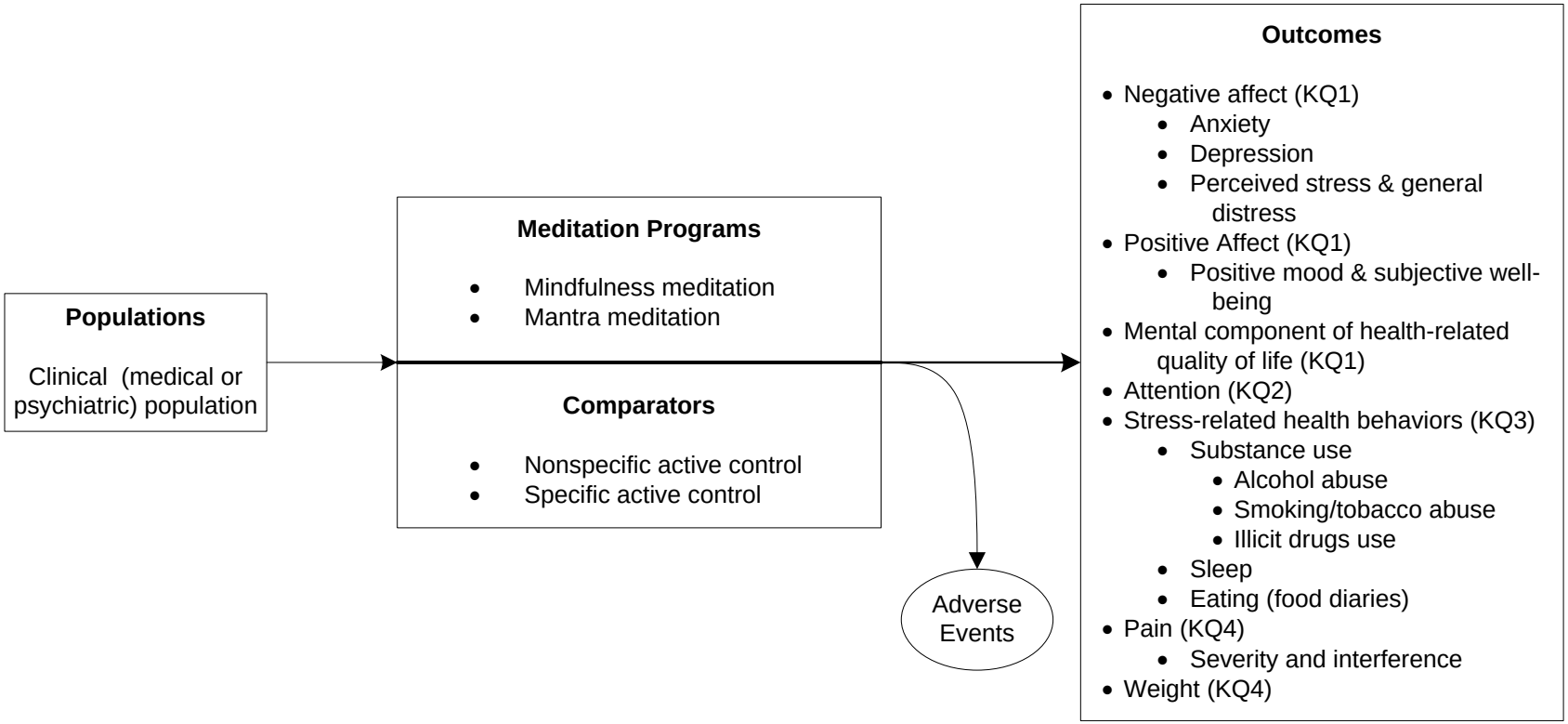

Figure 1: This figure depicts the key questions within the context of the PICOTS described in the previous section. Adverse events (AE) may occur at any point after the meditation program.

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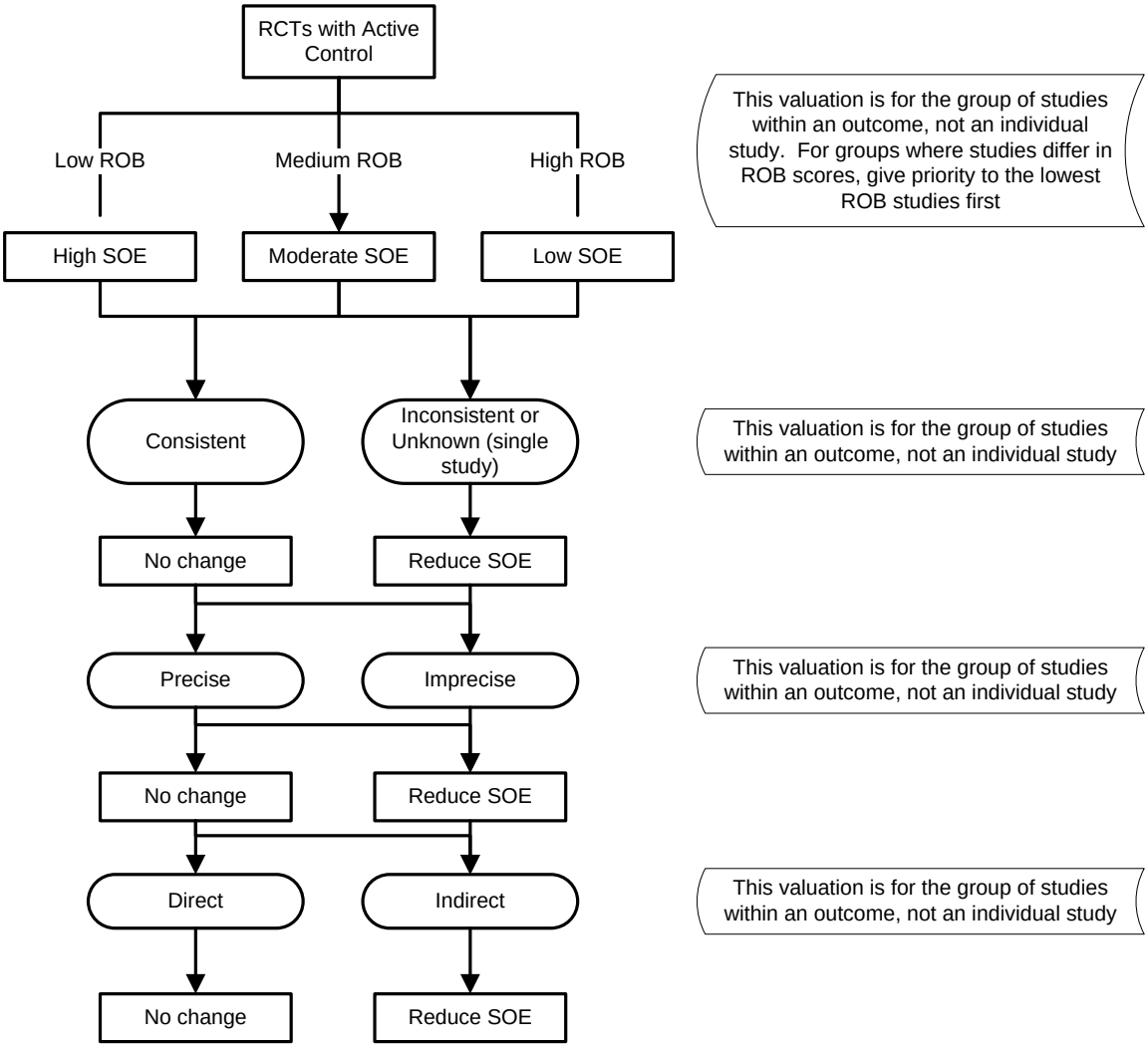
Figure 2: Algorithm for rating the Strength of Evidence



Definitions

Risk of Bias (ROB):	Low, Medium, or High based on 4 major and 4 minor criteria
Consistency:	The direction of effect, irrespective of statistical significance
Precision:	CI or p-values, prioritizing difference-in-change values or "group x time interaction" values
Directness:	If not a direct measure of an outcome, categorized as indirect

Assumptions

- All outcomes have at least 1 study
- Studies start out with a SOE grading based on ROB
- Then based on other criteria, they either maintain that SOE grade or are downgraded one notch. They do not upgrade.

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VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel to assure that the questions are specific and explicit about what information is being reviewed. In addition, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodologic experts who provide input in defining populations, approaches, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

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Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

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