NIH Collaboratory
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Health Care Systems Research Collaboratory

Regulatory/Ethics Consultation Call:

Group-Based Mindfulness For Patients With Chronic Low Back Pain In The Primary Care Setting (OPTIMUM)

Wednesday, December 18, 2019
Meeting Participants

Joe Ali (Johns Hopkins), Jeannie Barone (University of Pittsburgh), Judith Carrithers (Advarra), Susan Gaylord (UNC), John Lantos (Children's Mercy Hospital), Michelle LeMenager (University of Pittsburgh), Cathy Meyers (NCCIH), Stephanie Morain (Baylor College of Medicine), Natalia Morone (OPTIMUM PI, Boston Medical Center), Pearl O'Rourke (Retired from Partners Healthcare), Tammy Reece (Duke), Kayte Spector-Bagdady (University of Michigan), Jeremy Sugarman (Johns Hopkins), Wendy Weber (NCCIH), Gina Uhlenbrauck (Duke)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS

Overview of Demonstration Project	• **Overview:** The OPTIMUM pragmatic trial will evaluate a group-based mindfulness program for patients with chronic low back pain within primary care. Mindfulness is an effective treatment for chronic low back pain, yet it remains underutilized as it has not been regularly integrated into the outpatient clinical setting and is not reimbursed by health insurance companies. Mindfulness-based Stress Reduction (MBSR) is now recommended by the American College of Physicians for initial treatment of chronic low back pain. The goal of OPTIMUM is to inform decision makers about how this program can work in a real-life clinical setting and assess its impact on patient outcomes.
	
	 • **Collaborative network partners:**
	
	    ○ Boston Medical Center (BMC), Boston, MA
	    ○ Piedmont Health Services, in partnership with the University of North Carolina, Chapel Hill, NC
	    ○ University of Pittsburgh, Pittsburgh, PA
	
	 • **NIH Institute:** National Center for Complementary and Integrative Health (NCCIH)
	
	 • **Study design:** The OPTIMUM trial tests an evidence-based mindfulness intervention conducted at three partnering sites, two of which have a large	

AGENDA ITEMS	DISCUSSION	ACTION ITEMS
	proportion of patients from underserved or underrepresented populations (Boston Medical Center, Piedmont Health Services). In the UG3 phase, the trial will be piloted at each site with 5 patients. The study team expects to randomize 450 patients during the UH3 phase. The intervention consists of 8 weekly, 90-minute, group-based mindfulness sessions delivered in the primary care setting. Patient-level randomization and stratification will be by clinic and sex. Inclusion criteria are broad to include most patients referred for chronic low back pain to a primary care physician (PCP) at a participating practice. The two study arms will be the intervention plus usual care with the PCP compared with PCP usual care. Usual care consists of both pharmacologic and nonpharmacologic approaches. Questionnaires and follow-up will be the same for both study arms. • **Primary and secondary outcomes:** The primary patient outcome will be a 6-month assessment using the PEG scale (Pain, Enjoyment, General Activity). Secondary outcomes will be collected via the electronic health record (EHR), tracking healthcare utilization as indicated by opiate prescriptions, magnetic resonance imaging, injections, hospitalization, provider visits, emergency department visits, urgent care, PCP visits, physical therapy, and surgery. The PROMIS-29 mindfulness questionnaire will also be used to assess outcomes. This health-related quality of life assessment will include domains for depression, anxiety, physical function, sleep, and psychological measures.	
Status of IRB approval	• The University of Pittsburgh IRB is the single IRB of record for OPTIMUM. • The study team has obtained IRB approval for the UG3 phase. The team expects to work on the IRB application for the UH3 phase starting in Spring 2020. Boston Medical Center has been onboarded and UNC onboarding is pending.	
Risk classification	• The study team considers OPTIMUM to be a minimal risk study because it involves no medication, is evidence-based, and includes turning ordinary daily activities such as breathing and walking into a mindfulness meditation. • Those on the call agreed that the study appears to be minimal risk.	
Consent	• The study will obtain individual written informed consent from 5 participants at each site enrolled in the MBSR program for the UG3 pilot phase.	

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	• The consent process for the UH3 phase will involve individual written informed consent. However, the study team is interested in pursuing online consent for the UH3 phase and plans to work with the sIRB to implement. • It was confirmed on the call that the University of Pittsburgh IRB has reviewed and approved online consent for other studies under their purview.	
Privacy/HIPAA	• Participants are asked to sign the health system's confidentiality agreement for the group mindfulness sessions. • The team has obtained a partial waiver of HIPAA to recruit patients through the EHR. • The study team noted that CMS has clarified that it is acceptable for billing purposes for a clinician to address an individual patient in a group setting with other patients present in the group. • The study team will ensure that participants are reminded that the group mindfulness sessions are intended to be confidential, and request that all participants take action to maintain confidentiality and not disclose what is discussed within the sessions. • The PRO data for research will not be populated in the EHR. Research and medical data will be kept separate. • PRO data will be completed by the patients online, through email, or during office visits. • Those on the call discussed whether there might be clinical triggers (eg, suicidality, opioid abuse, depression) contained in the PROs that would prompt further action for notifying the patient's PCP. The study team noted that suicidality questions are not included in the PROs, but other questions might raise issues that warrant notifying the PCP and they will consider what such thresholds might be and including consent to contact the PCP in the final consent document. • Those on the call discussed questions around recruitment. The PI clarified that multiple methods will be needed, given differences in operations and workflows of the three health systems. The primary way of recruiting will be through the EHR. In the Boston system, the team is not intending to mail recruitment letters because in that setting, recruitment works best in-person within the clinic.	Tammy sent the link for the HEAL Initiative's data sharing policy to those on the call

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	• The PI clarified that clinic-based providers will be recruited through internal email and faculty presentations. • Regarding data sharing, the PI clarified that there is a central data repository at BMC, and a dedicated data team that will be using REDCap. Each site will have access to their own data but not the other sites' data. EHR data will be deidentified before going to BMC. • The NIH Project Officer will forward information to those on the call regarding requirements for public access and data sharing for HEAL/PRISM trials. There is a special repository used for HEAL/PRISM trials for deidentified data that meets privacy requirements. • The PI clarified that the single IRB process at the University of Pittsburgh involves assuring data security is in place.	(completed December 18, 2019): NIH HEAL Initiative Public Access and Data Sharing Policy: https://heal.nih.gov/about/public-access-data The Ethics and Regulatory Core will discuss this policy to identify any potential concerns specific to pragmatic clinical trials.
Monitoring and oversight	• The NIH Project Officer confirmed that for the UG3 pilot phase, no formal data and safety monitoring board (DSMB) is needed. • During the UH3 phase OPTIMUM plans to use a standard DSMB, with members who are not affiliated with the study.	
Issues beyond the study	• A certificate of confidentiality for the study will be automatically provided per new NIH policy. • The study team was encouraged to carefully review this certificate as they craft their final protocol, especially regarding protected health information. • Those on the call suggested that given that group medical visits are relatively new, the study provides an opportunity to systematically evaluate issues of privacy. It could be useful for future trials if the team devised a method of tracking how patients respond to group visits and whether there are feelings of invasion of privacy.	The Ethics and Regulatory Core will discuss issues related to privacy of group-level interventions in pragmatic clinical trials.

OPTIMUM

Chronic low back pain (cLBP) is one of the most common conditions treated in the primary care setting, yet treatment remains unsatisfactory for many patients. The opioid crisis has underscored the urgency of alleviating patients' cLBP with effective therapies, including evidence-based nonpharmacologic approaches. Mindfulness is effective for the treatment of cLBP yet remains underutilized as it has not been regularly woven into the outpatient clinical setting. Mindfulness-based Stress Reduction (MBSR) is now recommended by the American College of Physicians for initial treatment of cLBP. *The next necessary step is to do a pragmatic clinical trial (PCT) with the goal of informing decision makers how this program can work in a real-life clinical setting and its impact on outcomes.* We propose a PCT of this program titled **"OPTIMUM" (Optimizing Pain Treatment In Medical settings Using Mindfulness)**. It will be conducted with three health care system (HCS) sites (Boston Medical Center, MA, UPMC, Pittsburgh, PA, and Piedmont Health Services, in partnership with the University of North Carolina, Chapel Hill). *Our primary goal is to determine the impact of this intervention under usual care circumstances.* The *rationale* for this project is to inform key decision-makers how nonpharmacologic treatment can be integrated into routine care and the impact of this program on key outcomes. The **specific aims UG3 Phase** are the following: **Aim 1:** To plan and test a mindfulness clinical pain program, OPTIMUM, in the 3-HCS sites prior to the full PCT during the first 12-months of the project. Clearly defined milestones will be reached with guidance from the Collaboratory Coordinating Center. The **specific aims UH3 Phase are**: **Aim 2.** To integrate and test an evidence-based mindfulness clinical pain program, OPTIMUM, for patients with cLBP in the primary care setting. Four-hundred-

Chronic pain is one of the most common conditions treated in the primary care setting, with chronic low back pain (cLBP) costing over 30 billion dollars a year; yet treatment remains unsatisfactory for many patients.[1] The slippery slope of opioids to treat cLBP has many unintended consequences such as addiction, overdose, and diversion.[2,3] Compounding the problem, Primary Care Providers (PCP) have very little time during the 15-20 minute office visit to address the complex psychosocial and functional needs of the person with cLBP.[4] The opioid crisis has underscored the urgency of alleviating patients' cLBP with effective therapies, including evidence-based nonpharmacologic approaches that also address biopsychosocial needs.

Mindfulness is effective for the treatment of cLBP yet remains underutilized as it has not been regularly woven into the outpatient clinical setting and is not reimbursed by health insurance companies.[5,6] Mindfulness-based Stress Reduction (MBSR) is now part of the evidence-based guidelines of the American College of Physicians for initial treatment of cLBP.[7] We have shown that an 8-week program modeled on MBSR decreased pain and increased short-term function in older adults with cLBP.[5] *The next necessary step is to do a pragmatic clinical trial (PCT) with the goal of informing clinicians, patients, administrators and policy-makers how this program can work in a real-life clinical setting, impact outcomes, increase access to non-opioid treatments, and be reimbursable.* We propose an embedded PCT of this program titled **"OPTIMUM" (Optimizing Pain Treatment In Medical settings Using Mindfulness)**. It will be conducted with three health care system (HCS) sites (Boston Medical Center, MA, a safety net health system; UPMC, Pittsburgh, PA, a large health system; and Piedmont Health Services, NC, a network of federally funded health centers in partnership with the University of North Carolina (UNC), Chapel Hill). *Our primary goal for the PCT is to determine the impact of this intervention under usual care circumstances as defined in the FOA* (vs. implementation research). The investigative team has complementary strengths in PCT research, mindfulness and pain medicine, and is optimally positioned to carry out the PCT. The *rationale* for this project is to inform key decision-makers how nonpharmacologic treatment can be integrated into routine care and the impact of this integration on key outcomes. Our *long-term goal* is to increase the accessibility of evidence-based mindfulness programs to primary care patients with chronic pain. The **specific aims UG3 Phase** are the following:

Aim 1. To plan and test a mindfulness clinical pain program, OPTIMUM, in the 3-HCS sites prior to the full PCT during the first 12-months of the project.

Clearly defined milestones will be reached with guidance from the NIH Collaboratory Coordinating Center (CCC) and include: 1) identification of eligible patients with cLBP from the electronic health record (EHR), testing methods of recruitment, testing extraction of data from the EHR, building the database and testing for the collection of patient reported outcomes (PROs); 2) finalizing outcome measures and refining sample size with input from the Work Groups/CCC to improve rigor; 3) developing detailed implementation plans, training materials for clinicians and staff, standard operating procedures for embedding OPTIMUM into routine clinic work flows; 4) finalizing detailed data coordination and quality control for the UH3 phase; 5) piloting OPTIMUM with five patients at each site to finalize procedures to assure both smooth integration into clinic and collection of trial outcomes. Each OPTIMUM session will be facilitated by a trained MBSR teacher and a clinic-based provider (PCP or allied health professional).

The **specific aims UH3 Phase** are the following:

Aim 2. To integrate and test an evidence-based mindfulness clinical pain program, OPTIMUM, for patients with cLBP in the primary care setting.

Four-hundred-

We will assess integration of OPTIMUM into the clinic. We will determine PCP, patient, and practice satisfaction with these efforts.

RESOURCES AND DATA SHARING PLAN

Data Sharing within the Study
The OPTIMUM study team has extensive experience securely sharing and harmonizing data across multiple study sites, as evidenced by Dr. Morone and Dr. McTigue who were site multi-Principal Investigators (PI) for "Integrating Patient-Centered Exercise Coaching into Primary Care to Reduce Fragility Fractures" (PCORI PSC-1406-18325) for a three-site pragmatic trial which has enrolled 1130 patients. Additionally, Dr. McTigue is the lead PI of the PaTH Clinical Data Research Network. The PaTH Network is partially funded by the Patient-Centered Outcomes Research Institute (PCORI) and is one of 33 networks that comprise PCORI's National Patient-Centered Clinical Research Network (PCORnet). PaTH is comprised of seven academic health systems. PaTH data from the 13 sites comes from electronic health records, insurance claims data, directly reported data by people, and other data. As lead PI of PaTH Dr. McTigue has extensive experience securely sharing and harmonizing data across multiple health care systems.

Each health care systems (HCS) partner (Boston Medical Center, University of Pittsburgh Medical Center, and Piedmont Health Services; see letters of support) commits to facilitating access to all data sources relevant to the project. From the onset of project funding, the study team will work closely with the Collaboratory Coordinating Center (CCC) and other participating research sites to develop a clear, sustainable plan for data collection, data transfer and subsequent analyses through the Work Groups and to implement approved guidelines and practices for electronic data extraction and quality control methods and tools, as well as for electronic data sharing. In the planning phase, this will include developing and validating all electronic data methods and tools needed for the project, such as electronic health records (EHR) and patient reported data, and complete quality control testing at each HCS partner site.

Boston will serve as the central data collection and processing center and our efforts involving data sharing will be spearheaded by the Biostatistics and Epidemiology Data Analytic Center (BEDAC) at Boston University School of Public Health. Under the direction of the PI Dr. Morone and Co-Investigator Dr. Weinberg, BEDAC staff will be responsible for building the database for collection of patient-reported outcomes in REDCap, a HIPAA-compliant, web-based application for building and managing online databases available to the study team through the Boston University Clinical and Translational Science Institute. REDCap has proven to be a sophisticated yet easy-to use data entry system that provides customizable templates for use in clinical trial research. It allows for specific data quality measures to be implemented, including data verification and built-in data validation mechanisms such as logic and out of range data checks. Each site team will abide by its respective institution's procedures for obtaining data from the EHR, which will be used to both identify patients for trial recruitment and collect outcomes. Boston will serve as the central data collection and processing center. Institutional Review Board (IRB) approval, consent, and all regulatory requirements will be completed.

The OPTIMUM dataset will include data from 450 participants, including patient recorded outcomes such as pain, function and global impression of change. EHR data such as demographic data, health encounters (emergency department visits, hospitalizations, CT/MRI, opioid prescriptions), pain data (pain numeric rating scale, PEG) will also be obtained. Study data will be stored as SAS datasets; the datasets and documentation will be organized to allow for easy conversion to DDI (Data Documentation Initiative) format for archiving and sharing. At the moment, the project is not developing products with patent or trademark potential; however, should this become an issue in the future, our institutions are well equipped to facilitate this process in accordance with NIH regulations.

Data Sharing with the Public
In order to maximize the impact of this work, we will comply with all NIH policies and guidance related to data and research resource sharing, including the NIH Health Care Systems Research Collaboratory Data Sharing Policy, while protecting study subjects' rights to privacy and adhering to all appropriate state and federal confidentiality requirements and privacy guidelines (e.g., Health Information Portability and Accountability Act, HIPAA). This includes registering the trial at clinicaltrials.gov and reporting all results per NIH policy, as well as ensuring that all final peer-reviewed journal manuscripts that arise from these funds are submitted to PubMed Central immediately upon acceptance for publication. See Protection of Human Subjects for more detailed information about how privacy and confidentiality will be maintained.

The data generated by OPTIMUM, the methodologies used, and our findings will be made available in a timely manner to other researchers and those who have a legitimate purpose facilitating need for access. Although final datasets will be devoid of any specific identifiers prior to release for sharing, there is a small but finite possibility of deductive disclosure of subject identity with unusual characteristics. Therefore, the study team will make the data available to other investigators only after discussion and under a formal data-sharing agreement that provides for: (1) commitment to use data for research purposes only and not to identify individual study participants, further a lawsuit or legal claim against any individual or corporate entity, enhance corporate or individual financial gain or profit, or be used for any illegal purpose; (2) commitment to use appropriate information technology systems to keep data secure; and (3) commitment to returning or destroying data after analyses are complete. In addition, interested collaborators must outline their intended use of data with specific variables outlined and analyses described. Finally, data will only be shared provided IRB approval is obtained or evidence of IRB exemption is received. The study team will work with the Boston University Medical Campus IRB to assure protection of confidentiality, as necessary. Should a research subject be inadvertently identified, the investigator will immediately notify the OPTIMUM study team and destroy all files or copies of the data set in which any subject is identifiable. All publications which make use of OPTIMUM study data will acknowledge the source of the data and include appropriate grant numbers.

In the course of implementing the OPTIMUM study, a variety of questionnaires, policy and procedure manuals, and similar non-publishable research products will be developed, including research protocols and data collection instruments. We will make these materials available to other investigators with the following provisions:
1. That the OPTIMUM study, including appropriate grant numbers, be acknowledged in writing as the source of the material.
2. That the person requesting the material cover the administrative costs required, for example for copying, mailing, handling and other activities related to provision of the materials.
3. That the materials will not be used to enhance corporate or individual financial gain or profit.

The primary mode of data sharing will be through contributions at scientific meetings and timely publication of scientific accomplishments in peer-reviewed scientific journals, with technical appendices containing input data parameters whenever appropriate. Further, we will work with the communications teams at Boston Medical Center, Boston University School of Public Health, University of North Carolina at Chapel Hill and University of Pittsburgh to disseminate results and publication summaries in non-technical language to ensure reach to a broader audience. We will also share our findings with important medical and patient advocacy groups and policy decision makers, particularly as it relates to treating chronic low back pain. We will package the OPTIMUM materials (embedding into clinic, work flows, provider training) and make available to interested HCSs.

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August 7, 2019

Dear Dr. Weber,

Below is a written response to the items in Sections A and B of your letter dated July 30, 2019. We tried to keep our descriptions brief as was requested, but if further clarification is needed, please let us know.

   A.   Clarifications about the Proposed Study (provide a document addressing each item):

1. Based on our previous discussions, NCCIH understands that you have made the following modifications to your study:
a. The primary outcome measure will be changed to the PEG instead of the pain numeric rating scales.
b. The team will monitor the health care systems for new treatments or programs that may be rolled out for chronic pain during the course of the study.

2. Provide a brief description of how your project will account for the income generated by billing participants for the group medical visits at each of the sites. *It is important to note that the research project will not be paying patients to attend the group medical visits; they will only be paid to complete study questionnaires; we will pay the mindfulness instructor's salary out of the research grant, since the OPTIMUM program is "experimental". The Summary Statement had a Human Subjects concern, and that was that patients had to sign informed consent to take part in the 8-week OPTIMUM program. Therefore, participating in OPTIMUM is now part of the consent form. This is why we have labeled the OPTIMUM program experimental, although we note that it is evidence-based, is now recommended as first-line therapy for chronic low back pain, and it is what we will be teaching participants. Also, the research project will not be paying clinical providers to perform clinical services. The clinics will be billing insurance companies, including Medicare and Medicaid, for services rendered individually to patients by providers. This routine visit will occur before, during or after the group OPTIMUM program. Patients may pay a co-pay for the visit with the provider depending on their insurance requirements.*

For Boston Medical Center (BMC)/Boston University the study will be set up in the Velos system in which it is identified what visits (or parts of visits) are billable to insurers versus those billable to research. Participants are registered into Velos as they are enrolled so as to ensure billing is held and reviewed prior to charges being sent out. The BMC clinical trial office will reach out to the study team periodically as well should there be questions about a charge. The University of Pittsburgh conducts a fiscal review of all studies submitted for IRB approval. A separate account must be set up for all research related procedures that must be billed (for example, performing laboratory testing). Pittsburgh and Boston use the electronic medical record (EMR) "EPIC" system. The financial module of EPIC will also be used to track dates of services, provider billing, billed codes and procedures, and reimbursement. For the University of North Carolina, which is using Piedmont Health Services as the clinical site, the study will make use of Centricity 12.3, a joint EMR/billing system which tracks all patient care charges. Using this system, we will identify and track billable non-research clinical charges attributable to research-study participants, third-party reimbursements to the clinic, and out-of-pocket funds paid by research participants to the clinic for non-research clinical charges.

3. We previously discussed the timing of recruiting participants and when they will be randomized. Provide an overview of the timeline of when participants will be recruited and randomized to the study conditions (e.g. how long may participants have to wait for the next class before randomization): *The OPTIMUM program will last 8-weeks, therefore, if*

1

a potential participant is recruited at the beginning of the program and missed the first class they may have to wait for the next program to start two months later. Additionally, to build in time for potential delays in program start such as holidays we expect an interval of up to three months.

Specify whether participants will be randomized individually just before the classes start: *Participants will be randomized individually about one week before the classes start.*

Do you have any data about differential retention due to unmet expectations of those randomized to not get the MBSR treatment? *Yes, our R01 trial of 282 people randomized to an 8-week mindfulness program modeled on MBSR or an attention control reported those unsatisfied about their randomization assignment and so did not participate in the study. This was one person. Because of this experience we do not expect significant differential unmet expectations of those randomized to MBSR. The control group will still get reimbursed for their time filling out questionnaires and we believe this is one of the reasons they are likely to remain motivated to continue study participation.*

4. Your response to the summary statement mentions several distinct methods of recruitment may be used across the various health care systems. Please comment on whether this could cause differences in the types of patients that are recruited at the different health care systems. *There will be different recruitment methods since each site will be using methods that are successful for them in meeting the sample size goal. However, all participants will still be patients from the primary care clinics where the OPTIMUM program will take place. Because they will be patients from the clinic, and all clinics are primary care clinics we do not expect to see differences in the type of patients recruited. We are expecting differences in some of the demographic characteristics of the sample since UNC and Boston will be recruiting a primarily underserved population, but we believe this is a strength of the study.*

5. The context of usual care is going to be fluctuating over the course of the trial. How does the team plan to track changes in usual care in the different health care systems, since there may be regional differences? *We are tracking nonpharmacologic and pharmacologic treatments both by self-report and by querying each sites' methods of extracting healthcare utilization. Therefore, we will automatically track changes in treatment provided to participants. Additionally, each site has a provider-investigator that actively see patients. If they become aware of clinic wide initiatives to improve and/or change care for patients with chronic low back pain, they will be asked to notify the PI for the site, provide a description of the initiative, as well as the date the initiative started.*

It is also helpful for pragmatic trials to define what usual care is particularly when there may be differences between the health care systems. How will the team accomplish this? *We are already tracking non pharmacologic and pharmacologic treatments that make up usual care for chronic low back pain. Additionally, we will track office visits over the course of the 12-months participants are involved in the trial. A patient receiving usual care for chronic low back pain would typically see their provider for this issue 2-4 times a year and we will track this also.*

6. Do you plan to ask participants directly about medical utilization for their pain? Or will you rely on medical records from the participating health care systems? *We will do both. Medical records may not be complete if participants seek care outside of participating healthcare systems. Therefore, we will also ask participants directly about healthcare utilization.*

7. Will the team test extracting the necessary data from all three health systems during the UG3 phase and then the ability to merge this data? *Definitely. Since we know the variables needed we will work with the three health systems to establish and test the processes both to extract and then merge the data.*

8. Will the team collect information about other pain management treatments of self-care the participants may be engaged in both the MBSR and usual care arms (e.g. acupuncture, physical therapy, OTC pain medication, etc)? *Yes, we are asking about both non pharmacologic and pharmacologic therapies.*

9. Could you give us a brief description of the training plans for the MBSR and provider that will co-lead the intervention? The protocol or an SOP will need to be provided later with the full details, but a brief summary now would be helpful. *During the first year, each site will identify clinical billing providers and MBSR trained teachers (if not done so already) who will co-facilitate OPTIMUM. MBSR teachers will be experienced in teaching the 8-week program. The OPTIMUM program, modeled on MBSR, will require all identified MBSR-trained instructors to participate in four 1-hour*

training sessions via videoconference that will review the training manual in detail as well as review work flow procedures. Additionally, during the pilot program the MBSR instructors will meet weekly with Drs. Greco, Morone, and Gaylord to review each week and troubleshoot problems if they arise. During the UH3 phase monthly meetings will occur to review fidelity and quality control. Providers will also undergo training through video conference. This will be led by Drs. Gardiner and Dr. Morone. Content will include patient intakes, clinical care procedures, documentation in the EMR, and billing. The training will also make suggestions for the work flow procedures. Once the training is complete, providers will meet via videoconference after the first, 4th and 8th sessions during the pilot UG3 phase to review each week and troubleshoot problems if they arise. During the UH3 phase bimonthly meetings will occur with providers.

10. Will the team be able to track in real time the number of sessions participants attend in the intervention arm? This is important to be able to track in order to address major issues. *This will be collected directly in REDCap. We will require the MBSR instructors at each site to input this information after each weekly session.*

How much effort will the study employ to get good participation in the MBSR intervention? Note that we don't expect a plan that would be used in an explanatory trial, but we would like to know if you will have a plan to address adherence if one or more of the sites has challenges. *Having patients show up for appointments is a challenge for most clinical practices across the country-not only clinical trials. As a pragmatic trial we plan to remind patients of the upcoming appointments by engaging the routine clinic process of appointment reminders which may be a phone call, letter, or text. We will build in retention strategies from the outset by stating clearly to participants the expectation to attend weekly sessions. It is typical for clinics to do outreach to patients who have missed appointments with a phone call or letter. We will also employ these methods. If one of the sites is having challenges that another site is not having we will need to review their processes to assure they are all occurring as planned-such as patient reminders and program delivery.*

11. Statistical questions for the team:
a. You currently powered for 80% in your power calculations. For large scale trials such as this one we encourage using higher power such as 85-90% to determine the sample size. *With a sample size of 450 we have 90% power to detect a 1-point difference between groups on the PEG. One-point is considered a clinically significant group difference.*

b. Does the study plan to oversample any specific groups of population? *We are not planning to oversample a specific population. We are already recruiting an underserved population at the Boston and UNC sites.*

c. It is stated that randomization will be "stratified by clinic and sex". Does this actually mean stratification by site and sex, instead of by clinic and sex? *Yes, the latter is correct, the stratification is by site and sex.*

d. How will data collected during the UG3 phase on the 5 patients per site be analyzed? *We do not plan to analyze the data, we are collecting the data to identify glitches, errors, barriers, and problems with data collection that can be resolved before the UG3 phase.*

e. Does the study plan to use multiple imputation for missing data analyses? *Our primary approach to data analysis is based on mixed models which are more robust to missing data than traditional statistical methods. We will also conduct sensitivity analyses to explore the impact of missing data based on multiple imputation (gold standard) rather than single imputation.*

12. Milestone draft. NCCIH has provided comments and questions on your draft milestones in a separate document. Please address the proposed comments and send us a track changes version of the milestone document addressing our questions. *Track Changes document attached.*

B. Study Accrual and Retention Plan and Data and Safety Monitoring Plan
   1. *We will submit a detailed Study accrual and Retention Plan (SARP) prior to involving human subjects. We will be in close communication with Dr. Weber in developing a comprehensive and attainable SARP before formal submission to NCCIH as detailed in the clarification letter. We understand that throughout the conduct of the study, our progress will be regularly reviewed.*
   2. *A detailed DSMP will be created for the UG3 phase of the study, and we will follow the procedures outlined in the clarification letter, including providing a sample document and the CV or NIH Biosketches of three*

independent monitors. Participant enrollment will not begin until the DSMP has been approved by NCCIH and the IRB.

3. *We will register in ClinicalTrials.gov.*
4. *We will comply with reporting requirements including protocol amendments submitted to the NCCIH PO, submit enrollment reports beginning 4 months from the date of the Notice of Award, submit monitoring reports prepared for the independent monitors to the NCCIH PO, and the submit the final project report within 90 days of the project end date.*

As overall principal investigator for the proposed project, I confirm that all investigators will comply with the reporting requirements outlined in the clarification letter.

Sincerely,

Natalia E. Morone, MD, MS