Protocol

Effectiveness of a Mind-Body Program for Older Adults with Chronic Low Back Pain

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TABLE OF CONTENTS

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SYNOPSIS

Study Title

Effectiveness of a Mind-Body Program for Older Adults with Chronic Low Back Pain

Objectives

The aims of the study are the following: 1) to determine the effectiveness of a mind-body program in increasing function and reducing pain among older adults with chronic low back pain (CLBP), and 2) to evaluate the impact of mindfulness meditation on neuropsychological performance (NP) in older adults with CLBP.

Design and Outcomes

This experimental study is designed as a randomized, education controlled clinical trial of a mind-body program for older adults with CLBP. A sample of 300 independent, community-dwelling adults 65 years of age and older will be recruited. After determining eligibility, study participants will give written informed consent and study measures will be obtained. We will randomize participants into groups of 4 with no stratification using a software generated randomization plan. Participants in the mind-body group will receive the intervention of eight weekly 90-minute mindfulness meditation sessions that are modeled on the Mindfulness Based Stress Reduction (MBSR) program. Controls will receive an 8-week health education program based on the 10 Keys™ to Healthy Aging. After completion of the 8-week program, participants in the mind-body and education control program will be asked to return for 12 monthly booster sessions.

All participants will be assessed monthly over the telephone during and after the mind-body and education program with a subset of measures administered at baseline. Six and twelve months after the program is completed, participants will be asked to complete the entire set of measures again in person. Participants in the mind-body program will be asked to participate in focus groups between 6-12 months after program completion.

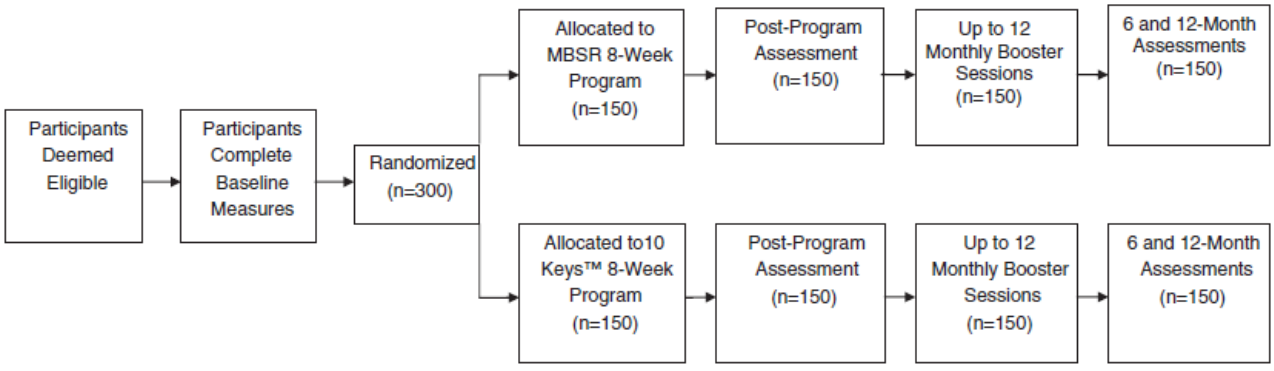

Fig. 1. Aging successfully with pain study design.

Interventions and Duration

Mind-body program
Frequency and setting: Participants will be seen in a group format once a week for 90 minutes for 8-weeks. Group size will be 10 participants per class. We found this to be the optimal class size in our pilot work because the group was small enough to encourage individual participation, but not too large that participants were afraid to talk.

The intervention will be modeled on the MBSR program. All sessions will be led by either Daniel Schenck or Carol Greco. Each has experience in teaching the MBSR program to older adults with chronic pain. Each has undergone teacher training in at least one intensive (≥ 50 hours) teacher training program conducted by the University of Massachusetts Medical School Center for Mindfulness. Daniel Schenck has practiced mindfulness meditation for 25 years and Carol Greco has practiced it for 14 years. All sessions will occur at the University of Pittsburgh Center for Research Health Care (CRHC), which has a large classroom, nearby parking, and is easily accessible by public transportation. Seniors may ride the public bus system for free in Pittsburgh.

Health education control program
A convincing comparison group is essential for participant recruitment and retention as well as essential to control for key components of the mind-body program. Therefore, the comparison group will control for time, group size, attention, homework, and facilitator time. We are basing the 8-week health education program on a successful aging curriculum known as the 10 Keys™ to Healthy Aging. Because this intervention teaches important health topics that are relevant to the older adult, it will provide a valuable program to participants. Pain information is not a component of the 10 Keys™ program, and we will not add this information to avoid contamination of the control group.

Total length of time each participant will be on study: 14 months.

Sample Size and Population
Our target sample size is 300 adults ≥ 65 years with chronic low back pain.

1. STUDY OBJECTIVES

1.1 Primary Objective

Specific Aim 1: To determine the effectiveness of a mind-body program in increasing function and reducing pain among older adults with chronic low back pain.

Primary Hypothesis: Mindfulness meditation will be associated with a clinically meaningful 2.5-point improvement in the Roland and Morris Disability Questionnaire, which is specific to the low back, immediately following an 8-week mind-body program as compared to an education control group.

Hypotheses 2: Compared to the control group, intervention participants will experience higher levels of functional status, decreased pain and increased psychological function immediately following the 8-week mind-body program.

Hypothesis 3: At 6 and 12 months follow-up, the magnitude of improvement in physical function, pain, and psychological function will be at least the same or improved since completion of the 8-week program.

1.2 Secondary Objectives

Specific Aim 2: To evaluate the impact of mindfulness meditation on neuropsychological performance (NP) in older adults with chronic low back pain.

Primary hypothesis 1: Mindfulness meditation will be associated with a significant improvement in the Tracking Test, part 2 of executive function immediately following an 8-week mind-body program as compared to an education control group.

Hypothesis 2: Improvement in executive function and attention will be significantly associated with improved physical function immediately following an 8-week mind-body program.

Hypothesis 3: Improvement in executive function and attention will mediate the relationship between pain and physical function.

Hypothesis 4: At 6 and 12 months follow-up, the magnitude of improvement in neuropsychological performance and physical function will be at least the same or improved since completion of the 8-week program.

2. BACKGROUND AND RATIONALE

Statement of the problem. Among the 37 million seniors alive today,[1] it is estimated that up to 50% of them live with chronic pain.[2] Greater than 17 million elders (≥ 65 years) have experienced at least one episode of low back pain (LBP) during the past year,[3] and it is the most frequently reported musculoskeletal problem.[4] Medicare data from 1991-2002 indicate that visits for LBP increased 132% and LBP charges increased 388%.[5] Pain is associated with a significant amount of morbidity in the older adult and includes decreased physical function, increased disability, decreased quality of life, poorer sleep, and depression.[6] Despite its prevalence and associated morbidities, many older adults suffer from inadequately treated pain. Why should this be the case?

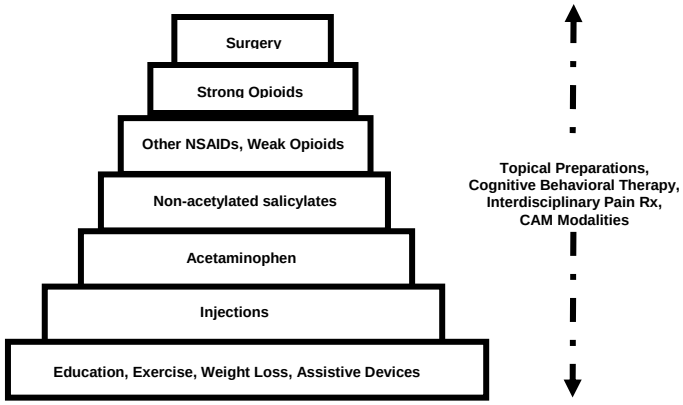

Figure 1. Stepped care approach used to treat pain

Because conventional treatment options are not always feasible for the older adult. Figure 1 shows a stepped care approach for the treatment of chronic pain in older adult patients.[7] Central to pain treatment is medication therapy with acetaminophen, non-steroidal anti-inflammatory agents (NSAID) and opioids. Yet these same medications are commonly toxic in the older population. NSAIDs are limited by their well-described gastrointestinal (GI) and nephrotoxic side-effects.[8] Narcotics are associated with an increased susceptibility to falls and hip fractures.[9] Even acetaminophen, typically used as the first medication to treat pain because of its general safety, is associated with GI side effects as in the large doses prescribed for pain (4 grams) it inhibits prostaglandin synthesis.[10,11] Surgery may be contraindicated in the frail older adult with multiple comorbidities. Traditional physical therapy approaches to persistent pain rehabilitation are often generically prescribed and focus on trying to ameliorate the direct effects of pain on the body (e.g., for chronic low back pain (CLBP), optimizing posture, body mechanics and spinal flexibility). When applied to older adults, these approaches do not appear to provide functional gains above and beyond that of analgesia alone.[12,13] Yet millions of individuals suffer from compromised quality of life because of frequent pain episodes.[3] There is an urgent need for safe and effective therapies to increase function and relieve chronic pain in the older adult. Our proposal centers on an 8-week mind-body program that we believe addresses this pressing need.

The rationale for mind-body therapies to treat chronic pain. The multidimensional nature of pain lends itself to the multidimensional approach of mind-body medicine. Pain researchers have long recognized the complexity of processing a painful stimulus, and have described not only a sensory component, but a cognitive and emotional component as well. Processing of a nociceptive stimulus involves sensory perception, and motivational and affective responses. In turn, mind-body therapies are based on a comprehensive approach to the patient that makes them singularly well-suited to address the various dimensions of pain. This approach is illustrated by the definition of mind-body medicine by the National Center for Complementary and Alternative Medicine (NCCAM):

> Mind-body medicine focuses on the interactions among the brain, mind, body, and behavior, and the powerful ways in which emotional, mental, social, spiritual, and behavioral factors can directly affect health. It regards as fundamental an approach that respects and enhances each person's capacity for self-knowledge and self-care, and it emphasizes techniques that are grounded in this approach.[14]

Because mind-body therapies such as mindfulness meditation teach patients to work with the sensory, cognitive and affective responses to pain, they can be especially applied to chronic pain patients. Additionally, because mind-body therapies do not involve medication, they offer a relatively safe treatment option for older adults who may have exhausted all other forms of pain therapy or for whom the risk of other therapy is unacceptably high. Our proposal will focus on a popular mind-body therapy called mindfulness meditation, which we have been able to successfully deliver to older adults with chronic low back pain. The intervention method we used is based on the 8-week Mindfulness-Based Stress Reduction (MBSR) program that has been studied widely in a younger population with a variety of medical conditions, but rarely chronic pain. Yet the holistic approach of mindfulness meditation described below makes it particularly well-suited to teach the older adult with chronic pain.

Mindfulness meditation as an adjunct treatment for chronic low back pain.

What is meditation? There are many forms of meditation that are used for medical purposes around the world. The two forms used commonly in the United States are mantra meditation and mindfulness meditation. These two forms of meditation have their origins in the East and have been adapted to a western audience and divorced from their original religious roots. Meditation has been difficult to define because there is more than one type of meditation that people have been practicing worldwide. Nevertheless, the Agency for Healthcare Research and Quality (AHRQ) published a 2007 report on Meditation Practices for Health and offered the following definition:

> A form of mental training that requires either stilling or emptying the mind, and that has as its goal a state of "detached observation" in which practitioners are aware of their environment, but do not become involved in thinking about it.[15]

What is mindfulness meditation? Kabat-Zinn, who first introduced mindfulness meditation to the medical community, described mindfulness simply as "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to the unfolding of experience moment by moment."[16] This is congruent with the consensus definition of meditation above. To elaborate on Kabat-Zinn's simple definition Shapiro[17] has proposed 3 aspects of mindfulness that include 1) the intention or purpose of practicing mindfulness that is set by the individual. This is varied, and depends on the person, 2) how attention is placed during the meditation. This involves focusing attention on an object like the breath, and continually bringing back the focus of attention to breathing when it is distracted. Thus, attention is as much bringing the awareness back to the breath when it has become distracted, as it is focusing on breathing, and 3) attitude, which describes the attitudes which support mindfulness and include being nonjudgmental toward thought or emotions or sensations as they arise, patience, non-striving, compassion, acceptance, and curiosity. Other supporting attitudes described have been letting go and trust.[18] Adopting these attitudes has also been described by Bishop in his description of mindfulness.[19] This theory of mindfulness is highly relevant to treating chronic pain. This is because it teaches chronic pain patients to uncouple the sensory from the cognitive and emotional responses to pain, which in turn may result in both increased function and pain reduction. We found this to be the case in our qualitative study.[20]

The three different methods of mindfulness meditation commonly taught take regular activities such as sitting, walking, and lying down and transform them into a meditation through directed breathing and mindful awareness of thoughts and sensations. The methods are: 1) the body scan, where in a lying position, the participant is guided to place their attention non-judgmentally on each area of the body from the toes to the top of the head, 2) sitting practice, which is focused attention on breathing while sitting on a chair or on a meditation cushion on the floor (for older adults, we only use a chair), 3) walking meditation, which is mindful slow walking with focused attention on body sensation and/or breathing and, 4) mindful movement as taught through yoga (but which we have changed to simple stretching exercises for older adults).

Evidence that mindfulness meditation helps reduce the experience of pain. Previous research of Kabat-Zinn of the MBSR program showed a significant reduction of chronic pain among 90 patients with a variety of chronic pain conditions.[21] He then published 4-year follow-up showing maintenance of pain improvement among 60-72% of 225 chronic pain patients.[22] The study by Kabat-Zinn did not include a comparison group. Sustained pain reduction up to 4-months after the MBSR intervention was noted in 20/28 fibromyalgia patients.[23] Thirty patients with musculoskeletal pain were randomized to an MBSR program, massage therapy or usual care. Significant improvement in mental health status but not pain reduction as compared to standard care occurred in the MBSR group.[24] Sixty-three patients with rheumatoid arthritis were

randomized to an MBSR program or a wait-list control program. Six-months after program completion, there was significant improvement in psychological distress and well-being.[25] Additionally, other studies have found that mindfulness meditation is associated with reduction in depression, anxiety, and stress.[26-28] Yet none of these studies targeted older adults or chronic low back pain except for our preliminary work. Although these results are compelling, **the studies had methodological problems as some lacked randomized controls, had small sample sizes, and included heterogeneous pain conditions and ages**. We plan to address these problems by conducting a large randomized, controlled trial focused on older adults with chronic low back pain with a sample size that has the power to detect differences between the two groups for our primary outcome measure.

The rationale for mindfulness meditation as therapy for treating pain. Mindfulness meditation provides a potentially safe, effective, nonpharmacologic, noninvasive, simple method for increased function and pain relief that could be used for the frailest older adult. Additionally, mindfulness meditation addresses the multiple dimensions that are affected by chronic pain.

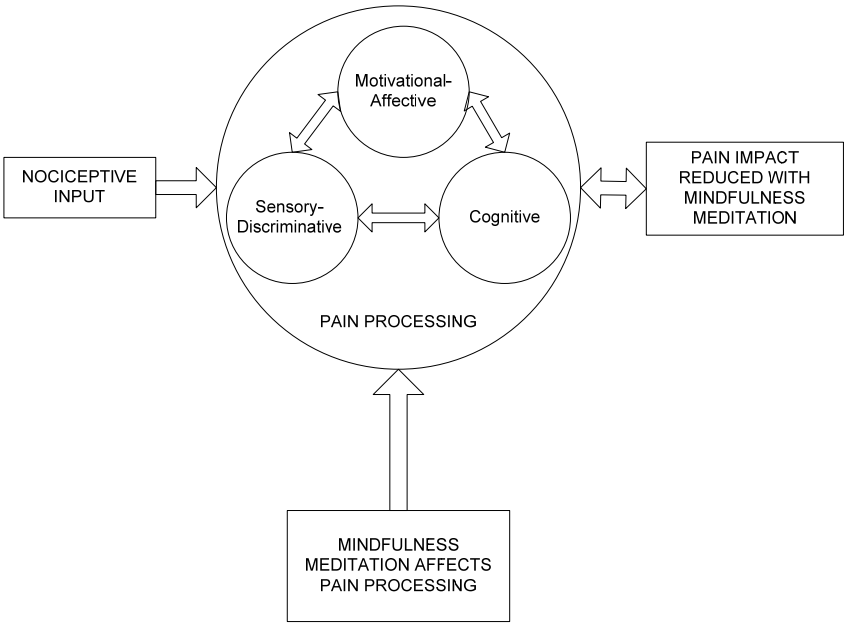

Figure. Model of mindfulness meditation's affect on pain processing. Meditation can affect all three areas of nociception, resulting in a potential decrease in the impact of pain on physical, psychological, and cognitive function.

In the proposed model (see adjacent figure), a nociceptive input is processed in the sensory, affective, and cognitive domains as proposed by Melzack. These areas also influence each other, and are why the arrows go in both directions. Mindfulness meditation can affect pain processing by possibly activating top-down inhibition of a nociceptive input. For example, the sensory-discriminative domain may be affected as a result of reduced muscle tension due to the relaxation response, with consequent reduction in the sensation of pain. The relaxation response is a hypometabolic state characterized by decreased heart rate, respiratory rate, and oxygen consumption, which is likely also associated with decreased muscle tension.[29,30] The affective domain of pain processing may be affected by improved coping with negative affective reactions, as well as enhanced general well-being. The cognitive domain may be affected as a result of recognizing habits or thoughts that may worsen pain. For example, participants in our study have recognized postures that they routinely used that increased pain. They have also recognized automatic thoughts about chronic pain and subsequent functional impact that were incorrect. For example, we found that participants have stopped using their canes as a result of the study, and increased their exercise capacity. The cognitive domain may also be affected by improved performance in attention and executive function, thus enhancing top-down regulation of pain.

Mindfulness meditation is a simple and safe method because it takes ordinary activities like breathing, eating and walking and turns them into a meditation by creating greater awareness of the moment-to-moment sensations, emotions, and thoughts that arise during these activities.[18,31] It is multidimensional because attention to sensory input can make the patient aware of postures or

behaviors that exacerbate the pain and decrease function. Improved NP (especially attention and executive function) may enhance top-down regulation of a painful stimulus. Attention to thoughts and emotions may raise awareness of relationships or habitual tendencies that exacerbate the pain because of the stress or negative reactions that are associated with them.[32] Modifying such negative reactions to pain is an important therapeutic goal as the emotional components of pain may have the effect of magnifying pain severity and a variety of other pain-related outcomes.[33] Although we focus on older adults with chronic pain because of the constellation of characteristics that makes mindfulness meditation particularly suitable for this population, results from this proposed study will have potential application for other forms of musculoskeletal pain in the older adult.

Are older adults interested in mind-body medicine? A nationally representative sample found that 19% of adults had used a mind-body therapy in the previous year and meditation was the most common therapy used.[34] Chronic pain was the third most common condition cited by respondents for which mind-body therapy was used. We found in our pilot work that older adults were enthusiastic about learning the meditation method and conscientious in attending classes. It is a disservice to the older adult to assume that they would not be open to learning meditation based on their age and indeed we found the opposite to be true.

How will mindfulness meditation change current practice? Current practice to treat chronic pain in older adults relies heavily on analgesics (pills or injections) and physical therapy. However, these treatments are limited because of toxicities (analgesics) or limited efficacy (physical therapy). Surgery is used for those with refractory pain, but failure rates are high and procedures morbid. Multidisciplinary pain clinics that take a holistic approach are not widely available and none focus on the older adult who has special needs. If we show the effectiveness of mindfulness meditation to improve function and reduce pain, this result has the potential to add another option to pain rehabilitation in the older adult that is safe and accessible. Referral to an 8-week mind-body program would be an option that could be offered to patients. The MBSR program is already offered by 476 practitioners worldwide, and the modifications we have made to the program to address the needs of older adults with chronic pain are simple to incorporate.[35]

Sustained improvement over time. Included in instructions for meditation (regardless of tradition), is the emphasis on regular meditation practice.[36] This is because it takes time to develop familiarity with meditation, and proficiency and beneficial effects are presumed to take time to occur. Yet mindfulness meditation studies typically focus on results from a brief 8-week MBSR program, which in and of itself is only an introduction to meditation. Acknowledging this, most MBSR programs offer regularly scheduled (e.g., monthly) "booster" classes. Empirical studies that have followed participants over time show support for this idea. Teasdale and Ma have shown that mindfulness-based cognitive therapy in non-depressed patients with a history of three or more episodes of depression reduced relapse by 39% and 42% respectively at 12-months after program completion as compared to a treatment-as-usual group.[37] Pradhan in her study of MBSR for patients with rheumatoid arthritis found no statistically significant changes at program completion, but did find statistical significance for measures of psychological distress and well-being at 6-months, compared to a wait-list control group.[25] Both studies had a maintenance program after the initial 8-week program. In Mackenzie's qualitative study of oncology patients who attended a post-MBSR program drop-in group one participant stated, "The 8-week programme was a preparation for what we've been doing since. I can't say I didn't get a lot out of the initial program, because I did, but looking back I got relatively little out of it compared to what I've got from the drop-in group. I feel sorry for people who do the 8-week programme and don't continue on. The benefit for me has come in the long term. Things keep happening, little bits here and there. The 8-week programme was just a start."[38] Our pilot work also supports these findings as one participant stated, "The full effectiveness of the meditation program is a continuity of practice over a lifetime."[20]

Anecdotally, we found that three participants in our pilot work discontinued using their canes. One did it by class 1, one by class 5, and another by class 8. This heterogeneity in response is not unexpected in a mind-body program since each individual will take their own time to understand the mind-body concepts being presented and put them into practice. Because of the likely importance of regular booster sessions for participants to receive the full benefit of mindfulness meditation, we propose to hold monthly booster sessions for up to 12 months for participants randomized to the 8-week mind-body program. We did not hold booster sessions during our pilot trial and believe this is an important addition to our proposed study.

Mindfulness meditation as a method to improve neuropsychological performance

Evidence that mindfulness meditation may improve neuropsychological performance. Because of the emphasis of mindfulness meditation on sharpening one's attention to the present moment's experience, researchers have been actively studying its effects on neuropsychological performance. One aspect of NP is attention. Attention is divided into alerting, orienting, and conflict monitoring aspects. A study by Jha[39] tested these three aspects by comparing a healthy population who took the 8-week MBSR program, to experienced meditators who underwent a month-long mindfulness meditation retreat, to a control group. She found that at baseline, retreat participants had better conflict monitoring scores, while at time 2, after the 8-week MBSR program, MBSR participants had better orienting scores than the other two groups, and retreat participants had better alerting scores. This study suggests that even a short 8-week MBSR program may affect change in attention. This is consistent with our pilot work that showed after an 8-week MBSR program, attention trended to improvement as measured by the Digit Symbol Substitution Test and self-report "concentration" improved for many participants. In addition to attention, executive function is also an important neuropsychological ability which can be tested with the Stroop task. This common test was used by Wenk-Sormaz among healthy college students. Students who did mindfulness meditation as compared to an active or passive control performed better on the Stroop.[40] Because of mindfulness meditation's promising potential to affect NP, we will measure two domains of NP (attention and executive function) in the proposed study through an innovative software program (the CAMCI). Improving NP may be one of the mechanisms by which mindfulness meditation works. We will explore these possibilities in our analysis by determining whether baseline attention and executive function predicts outcome in physical function and pain relief, as well as whether change in attention and executive function predicts the same.

The link between neuropsychological performance and physical function. The association between dementia and decreased physical function has been well-established and has been shown to be associated with mobility impairment,[41] task-specific disability,[42] and progressive functional decline.[43,44] There is evidence that an association between neuropsychological performance and physical function is also present in cognitively intact individuals. Binder and colleagues demonstrated, in 125 cognitively intact older adults with unknown pain status enrolled in a randomized trial of exercise or hormone replacement therapy,[45] that cognitive processing speed predicted physical frailty as measured by a modified physical performance test. Ble and colleagues demonstrated a relationship between executive function and gait velocity on an obstacle course in participants of the InCHIANTI study.[46] Rosano and colleagues found, in a large cohort of high-functioning older adults, that gait speed was associated with cognitive function after controlling for important covariates.[47] Tabbarah and colleagues, in a 7 year longitudinal study of community dwelling older adults, found an association between NP decline and declines in mobility and routine task performance (e.g., walking at a normal pace) and more challenging task performance (e.g., tandem stance, fast walking).[48]

Because we have evidence that mindfulness meditation may improve NP, our secondary aim is to investigate the relationship between NP and physical function in older adults who have participated in the mind-body program vs. controls. Improved NP as a result of mindfulness meditation may prove to be an important underlying mechanism of action of mindfulness. Improved performance may also distinguish those who benefit from learning the mind-body method from those who do not.

The link between neuropsychological performance, pain and physical function. We have found that in community dwelling older adult patients with heterogeneous persistent non-malignant pain disorders, pain severity was associated with diminished executive function.[49] In older adults with CLBP we have found decrements in multiple domains of NP as compared with pain-free age-matched controls, specifically immediate and delayed memory, language, executive function, and manual dexterity.[50] As anticipated, significant inverse relationships between pain severity and NP and between pain severity and physical performance were demonstrated.

An unexpected finding was that the association between pain severity and physical performance was no longer significant when analyses controlled for NP, suggesting NP mediated the relationship between pain severity and physical performance. Therefore, even with more severe pain, if NP was high, there was not an effect on physical function. If, indeed, NP mediates the relationship between pain and disability, perhaps persistent pain-associated disability and the approach to its rehabilitation should be reconceptualized for older adults. Perhaps, for example, cognitive retraining (i.e., improving or restoring a person's skills in the areas of paying attention, remembering, organizing, reasoning and understanding, problem-solving, decision-making, and higher level cognitive abilities) should be incorporated as one component of efforts to rehabilitate older adults with persistent pain. We believe that mindfulness meditation as delivered through the 8-week mind-body program that is the core of this proposal has this potential.

Chronic low back pain is common among older adults and frequently undertreated. Mind-body therapies have the potential to fill the need for safe treatment of pain and resultant decreased function in the older adult since they have few side-effects. Mindfulness meditation is one of these therapies and is at the core of this proposal. It is particularly well-suited to the older adult both in theory and practice because it addresses the multidimensional nature of pain and its consequences and is at the same time a safe and gentle method that can be taught to older adults without an upper age limit. Despite this promising potential, large, randomized controlled studies have not been done in the older adult with chronic pain to evaluate its effectiveness. Our proposal has great potential for significance as 1) it will be the first large, rigorously designed, randomized controlled trial of a mind-body intervention for older adults with chronic low back pain. This population has been largely ignored in mind-body pain research, 2) mindfulness meditation is well-suited to the older adult with chronic pain, 3) neuropsychological performance may improve with mindfulness meditation but this effect has not been studied in older adults outside of our pilot work.

2.1 Study Rationale

We have shown that an 8-week mind-body program that teaches mindfulness meditation to older adults with CLBP is feasible and may be beneficial as a therapeutic adjunct to conventional pain therapy. Because of the lack of large, rigorous clinical trials in older adults in mind-body medicine in general, and meditation in particular,[36,51] the conduct of a large, well-designed, randomized controlled trial in older adults with CLBP will add significantly to our understanding of the effectiveness of mindfulness meditation on the varied physical, cognitive, and psychological aspects of chronic pain in older adults.

Preliminary Work Related To Specific Aim 1

The impact of chronic low back pain on the older adult. We conducted a secondary data analysis of the psychological and physical characteristics of older adults with chronic low back pain vs. knee osteoarthritis (OA), two common musculoskeletal disorders in the aging adult. We found that participants with CLBP had significantly slower gait speed (0.88 m/sec vs. 0.96 m/sec, p=0.002) and significantly more comorbid conditions than participants with chronic knee OA.[52] Additionally, CLBP participants had significantly worse scores on psychological measures of depression, self-efficacy, fear-avoidance, and pain catastrophizing. Older adults with chronic low back pain have distinct psychological and physical profiles, with the burden of illness appearing greater for them. In another study among 2,766 community-dwelling older adults we found that the frequency and intensity of low back pain was associated with self-reported difficulty in common functional tasks such as stooping and pulling/pushing. Additionally, as pain frequency/intensity worsened so did self-reported functional difficulty in some tasks suggesting a "dose-response" relationship between pain and physical function.[53] Given both the psychological and physical burden of CLPB the mind-body program we propose to deliver will provide a unique opportunity for participants to increase their ability to cope with chronic pain and its physical and psychological consequences.

Outcome Measure	Group[a]	Baseline mean ± SD	8-Week mean ± SD	Effect Size d [b]	P-value	3-Month follow-up, meditation group only mean ± SD
Pain						
McGill Pain Questionnaire-Short Form[c]	Meditation Control	15.5 ± 10.0 15.2 ± 7.0	13.7 ± 7.9 15.7 ± 9.1	0.32	0.16	16.5 ± 11.6[d]
SF-36 Pain Scale	Meditation Control	35.5 ± 6.0 35.7 ± 7.2	39.9 ± 7.7 38.8 ± 8.3	0.16	0.31	39.9 ± 8.4[d]
Physical Function						
Roland Disability Questionnaire[b]	Meditation Control	11.5 ± 3.7 11.8 ± 4.6	9.4 ± 5.1 10.6 ± 5.3	0.35	0.25	8.9 ± 5.7[d]
SF-36 Physical Function Scale	Meditation Control	42.0 ± 10.9 45.1 ± 9.5	45.7 ± 9.2 44.5 ± 10.1	0.46	0.03	45.8 ± 11.5[d]
Psychological Function						
Chronic Pain Acceptance Questionnaire Total Score	Meditation Control	72.2 ± 13.4 68.1 ± 20.3	75.5 ± 16.0 64.8 ± 23.0	0.83	0.008	74.5 ± 15.9[d]

[a]Meditation n = 19, control n= 18, except for the attention measures n =18 both groups.
[b]d=M_t -M_c / σ_{pooled}. M_t = mean change score for the treatment group, M_c = mean change score for the control group, $\sigma_{pooled} = \sqrt{[\sigma_t^2 + \sigma_c^2 / 2]}$, σ_t = standard deviation of change score for treatment group, σ_c = standard deviation of change score for control group.
[c]Lower scores indicate improvement.
[d]No statistically significant difference (P>.05) between 8-week and 3-month scores with one sample t-test.

Mindfulness meditation randomized controlled pilot study. Mindfulness meditation had not been studied exclusively in older adults with chronic pain prior to our work. Because of this, while planning we decided to study the feasibility of using mindfulness meditation to treat older adults who were are least 65 years old and who had chronic low back pain.[54] Given the lack of randomized controlled trials of mind-body medicine in older adults[51] we decided to carry out a randomized, wait-list controlled

study and modeled the intervention on the Mindfulness-Based Stress Reduction Program. This program has been well-described in the literature and because it has been operationalized lends itself well to a study protocol.[18]

We were able to screen 89 older adults and recruit 37 of them into the study within a 6-month period despite limited resources. We found that these independent, community-dwelling older adults were enthusiastic about participating in the study and consistently reliable in attending classes, as well as completing pre and post assessments. Participants met weekly for 90-minute sessions. They were requested to meditate 6 of 7 days a week for 45 minutes a day. Chronic low back pain was defined as moderate pain occurring daily or almost every day for at least the previous three months. Baseline, 8-week and 3-month follow-up measures of pain, physical function and quality of life were assessed. Meditation diaries recorded comments of participants and time spent meditating daily. Briefly, the results were the following: descriptive statistics revealed no significant baseline differences in age, gender, race, income or level of education between groups. No adverse events occurred during the intervention. The mean age of the sample was 74.9 years, 21/37 (57%) of participants were female and 33/37 (89%) were white. At the end of the intervention, 30/37 (81%) of participants completed 8-week assessments. Average class attendance in the intervention arm was 6.7. They meditated an average of 4.3 days a week and the average minutes per day was 31.6. Compared to the control group, the intervention group displayed significant improvement in physical function as measured by the SF-36 Physical Function Scale ($P = .03$, effect size = .46) and pain acceptance as measured by the Chronic Pain Acceptance Questionnaire ($P = .008$, effect size = .83). There was a trend toward pain reduction as measured by the McGill Pain Questionnaire-Short Form (effect size = .32, $P = .16$).

There were a total of 25 participants assessed for the 3-month follow-up. Nineteen (76%) continued to meditate, 18 (72%) had recommended the class to others, 16 (64%) reported they could "concentrate better" and 12 (48%) reported taking less medication for pain or sleep. See Table above for further details. After completion of this trial, we were confident that an 8-week mind-body program was feasible for older adults and held promising potential as an adjuvant treatment for chronic pain.

The next step and the focus of the proposed research, is to conduct a large clinical trial to more definitively answer the question of the effectiveness of meditation to improve function, reduce pain, and to illuminate which aspects of pain (sensory, cognitive, emotional) meditation has the greatest impact.

Mindfulness meditation qualitative study. The diaries filled out by participants in the above pilot study held a large amount of detailed descriptions of the experience of learning mindfulness meditation and applying it to pain and daily life. Because of this, we conducted a qualitative study of the diary entries. Twenty-seven participants filled out a daily diary of their experience. The mean number of participants who handed in a diary every week was 18 (range 10-26). Including their comments about the class at 3-month follow-up, there were 742 lines of text available for

Themes	Example
Distraction from pain	"I have known for years that distraction made me forget my pain to a great extent...with mindfulness I can concentrate on prayer, music, exercise, and probably many other things that distract me from the pain. This is something I did not realize on my own."
Heightened awareness of pain sensation leading to behavior change	"I learned to stop when the pain starts up."
Better coping with pain	"The pain is still with me; however, it just doesn't feel as intense as it was. I feel results of the study and the practice is having a positive effect."
Direct elimination of pain	"By using meditation I have been able to reduce the feeling of pain."
Improved attention	"Benefits of clearer thinking/focusing continue."
Short-term effects	"When I finished the meditation I felt like a new person."
Long-term effects	"This program has really changed my life. Because of the meditation, I not only have less back pain, I am more aware of my life and am learning to live it to the fullest."

analysis. An analytic approach based on grounded theory was used.

The following themes were identified from the text: distraction from pain, heightened awareness of pain, direct elimination of pain, improved attention, short-term effects, long-term effects. The adjacent table provides illustrative quotes for each theme. Mindfulness meditation had beneficial effects on pain, attention, sleep, and well-being in older adults who experience chronic low back pain. Various methods of pain reduction were used, including distraction, increased body awareness leading to behavior change, better coping skills, imagery, and direct pain reduction through meditation. Sleep latency was improved as well as quality of sleep. Participants described well-being during and after a meditation session that had immediate effects on mood elevation but also lasting global effects on quality of life.

The first person accounts of the experience of mindfulness meditation in older adults with chronic pain allowed us to describe effects that could not be captured by quantitative techniques. Because of this finding, we are including a qualitative evaluation in this grant proposal to capture in-depth personal narratives that will shed light on the experience of learning and applying mindfulness meditation to chronic pain and daily life. We will strengthen the qualitative approach by conducting focus groups that will allow us to extensively explore the participants' experience with working with pain that will provide more in-depth information than the diary entries. This is because the diary entries were open-ended, and did not ask specifically about working with pain.

Mind-body research in older adults. We conducted a structured review of eight mind-body therapies for chronic non-malignant pain in older adults.[51] Sadly, we found this was a largely neglected area of research. There was a surprising lack of randomized controlled trials in seniors (we found only two), and, given this, were forced to include a younger population in the review (50 years of age and above). Most studies were limited by small sample size, lacked randomization, and lacked a control group. Yet, we found the therapies feasible and safe for this population. Given the potential of mind-body therapies as an adjunct treatment for pain as well as the popularity of these therapies among older adults,[55,56] there is a clear need for large, well-designed, controlled, clinical trials. Our proposed study will contribute significantly to our understanding of the effects of meditation on chronic pain in the older adult as well as address many of the design issues that have plagued mind-body research in this population.

Preliminary Work Related To Specific Aim 2

The connection between pain, physical function, and neuropsychological performance (NP). Until recently, neither the relationship between chronic nonmalignant pain and NP nor the role that NP plays in mediating the relationship between chronic pain and physical function, had been investigated in older adults. We recently did so in 163 CLBP and 160 pain-free community dwelling older adults.[57] Significant between-group differences in NP scores were found, particularly with regard to immediate and delayed memory, language, mental flexibility, and motor speed. In both

Comparison of the Effects of Meditation versus Wait-List Control in Outcomes During the 8-Week Trial and 3-Month Follow-Up

Outcome Measure	Group[a]	Baseline mean ± SD	8-Week mean ± SD	Effect Size *d* [b]	P-value	3-Month follow-up, meditation group only mean ± SD
Trails A[c]	Meditation Control	45.5 ±14.6 37.5 ±10.1	41.2 ± 11.9 40.5 ± 14.2	0.67	0.027	41.8 ± 10.9 [d]
Digit Symbol Substitution Test[e]	Meditation Control	52.6 ± 14.7 58.7 ± 9.0	54.6 ± 13.0 58.3 ±13.4	0.29	0.20	55.7 ± 15.1[d]

[a]Meditation n = 19, control n= 18, except for the attention measures n =18 both groups.
[b]$d = M_t - M_c / \sigma_{pooled}$. M_t = mean change score for the treatment group, M_c = mean change score for the control group, $\sigma_{pooled} = \sqrt{[\sigma_t^2 + \sigma_c^2 / 2]}$, σ_t = standard deviation of change score for treatment group, σ_c = standard deviation of change score for control group.
[c]Lower scores indicate improvement.
[d]No statistically significant difference ($P>.05$) between 8-week and 3-month scores with one sample *t*-test.
[e]Higher scores indicate improvement.

CLBP and pain-free participants, NP scores were significantly correlated with gait speed and functional reach but not with timed chair rise, trunk rotation, self-reported disability, or psychopathology (e.g., depression). Within-group analyses revealed that NP- specifically the domains of attention, visuospatial skills, executive function, and psychomotor speed-was correlated with pain intensity and that after controlling for NP, the relationship between pain and physical performance was no longer significant. This suggests either that NP mediates the relationship between pain and physical performance, or that physical performance and NP are highly linked in some way (i.e., via the brain).

The effect of mindfulness meditation on neuropsychological performance. We measured NP in our pilot clinical trial described above using two well-known measures, the Trails A which measures attention and psychomotor speed, and the Digit Symbol Substitution Test (DSST) which measures executive function (see Table). Note that at the 3-month follow-up only the meditation group was reported as the control group had already crossed over and received the meditation program. There was significant improvement in the Trails A score. While the DSST did not reach statistical significance, the results were in the expected direction, with a small effect size. Although there are differences at baseline in the scores of the meditation and control groups, these differences are not statistically significant. These preliminary results have prompted us to take the next step and measure the attention and executive function domains of NP more extensively in the proposed study as mindfulness meditation may have the potential to cognitively retrain the older adult with chronic pain. Improved NP may prove to be one of the mechanisms of action of mindfulness meditation. Baseline NP scores may also help distinguish responders from non-responders.

The Computer-Based Assessment of Mild Cognitive Impairment (CAMCI). We have developed a brief, standardized, computer-based assessment of mental status that assesses the NP domains of executive function and attention. Results from a sample of over 500 community dwelling adults age 65 and older have shown that the CAMCI can discriminate between persons with mild changes in cognition from healthy elderly.[58-60] The sensitivity and specificity of the CAMCI in determining cognitive status (normal vs mild cognitive impairment) is high (78 and 82, respectively).

Among pain-free individuals, we investigated the relationship between physical function and cognition among 96 African American community dwelling older adults aged 60 and above. To evaluate cognitive function we used the CAMCI. We found that decreased executive function predicted decreased lower extremity physical function as measured objectively with the well-known Short Physical Performance Battery.[60] This suggested NP was independently associated with physical function. Because of this association of executive function and physical function, as well as our findings of the relationship of executive function, physical function and pain, we are using the Tracking Test, part 2 measure of executive function to test our primary hypothesis for Aim 2.

Summary and conclusions. Preliminary data collected by our group demonstrate that a mind-body program of mindfulness meditation is feasible among older adults with CLBP and may be an effective adjunct treatment for increasing function and decreasing pain. Additionally, it may have beneficial effects on NP. However, a larger trial with longer follow-up is necessary before recommendations can be made about its clinical application. The preliminary studies, taken together, combined with our collective experience in evaluating and treating older adults with chronic pain, design, and implementation of clinical trials, development of neuropsychological batteries in the older adult, delivering the mind-body program, and community-based research has been invaluable in shaping the design of our intervention. The assembled team will be a key

resource in implementing the proposed study. Our experience in performing clinical trials and in analyzing complex data sets makes the likelihood of completing the proposed work very high, and will allow us to interpret the findings of the study with sophistication.

3. STUDY DESIGN

This experimental study is designed as a randomized, education controlled clinical trial of a mind-body program for older adults with CLBP. A sample of 300 independent, community-dwelling adults 65 years of age and older will be recruited. After determining eligibility, study participants will give written informed consent and study measures will be obtained. We will randomize participants into groups of 10 with no stratification using a software generated randomization plan. Participants in the mind-body group will receive the intervention of eight weekly 90-minute mindfulness meditation sessions that are modeled on the MBSR program. We have piloted the program and demonstrated its feasibility among older adults with CLBP and have preliminary evidence of the effectiveness of the program.[54] Controls will receive an 8-week health education program based on the 10 Keys™ to Healthy Aging. After completion of the 8-week program, participants in the mind-body and education control program will be asked to return for 12 monthly booster sessions.

All participants will be assessed monthly over the telephone during and after the mind-body and education program with a subset of measures administered at baseline. Six and twelve months after the program is completed, participants will be asked to complete the entire set of measures again in person. Participants in the mind-body program will be asked to participate in focus groups between 6-12 months after program completion.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

All participants will be **included** if they are:

1) 65 years of age or older.

2) Have intact cognition (MMSE >24).

3) Have functional limitations due to their low back, defined as a score of at least 11 on the Roland and Morris Disability Questionnaire.

4) CLBP, defined as moderate pain occurring daily or almost every day for at least the previous three months.

5) Speak English.

4.2 Exclusion Criteria

Participants will be **excluded** if they:

1) Do not meet the above inclusion criteria.

2) Have previously participated in a mindfulness meditation program.

3) Have serious underlying illness (like malignancy, infection, unexplained fever, weight loss or recent trauma) causing their pain.

4) Are non-ambulatory, or have severely impaired mobility (i.e., require the use of a walker): since measurement of physical performance in the proposed study includes timed chair rise, gait velocity, and standing balance, conditions other than back pain that could negatively impact these measures may confound our study results.

5) Have severe visual or hearing impairment: since this study will involve questionnaires and telephone evaluations, severe visual and/or hearing impairments may interfere with data collection and data validity. For example, the Mini-Mental Status Exam has never been validated in those with severe visual or hearing disturbance.

6) Have pain in other parts of the body that is more severe than their low back pain, defined as pain other than in the lower back that occurs daily or almost every day and is of at least moderate intensity or acute back pain: since we will be specifically evaluating chronic low back pain, we do not want to confound the outcome data with significant pain from other areas or with acute pain. Thus only participants with chronic low back pain severity that is greater than pain severity elsewhere in the body will be included.

7) Have acute or terminal illness: To insure weekly participation and a twelve month follow-up, participants with an acute or terminal illness will be excluded from the study.

8) Have moderate to severe depression, defined as a Geriatric Depression Scale score of 21 and above: since active depression may affect the psychological outcomes of the study and may affect compliance with participation in the intervention and control programs.

9) Do not have access to a telephone: since monthly assessments will be done over the telephone**.**

4.3 Study Enrollment Procedures

Recruitment. We will recruit study participants from the University of Pittsburgh Pepper Research Registry (made up of community-dwelling older adults from the greater Pittsburgh area), University of Pittsburgh alumni mailing list, direct purchase of addresses from a direct mail business, the UPMC General Internal Medicine Clinic and its research registry, posted flyers, radio, bus, and newspaper advertisements. We will be able to take advantage of the research registry available at the University of Pittsburgh Physicians, General Internal Medicine Clinic. The PI also has a clinical practice in this clinic. In addition to the registry, the General Internal Medicine Clinic employs a full-time research recruiter. When patients arrive in clinic for an appointment, they are all given a self-administered computerized intake form, delivered on a tablet PC, to answer routine medical questions before their encounter. We will be able to ask all older adults via the tablet whether they have low back pain and whether they are interested in hearing about a study for patients who have low back pain. All those who mark yes on the tablet will be

approached that day by the research recruiter and the preliminary screening will be done. The clinic sees an average of 180 patients/week of which 18% are older adults. Thus, potentially 32 patients/week will be asked about their interest in the study. This procedure is well-established in the clinic and has been successfully implemented by investigators to recruit research participants.[61] For recruitment, we will also have the advantage of having the large geriatric population in the greater Pittsburgh area, which has a larger than average population compared to the rest of the country.[62-64] We found older adults are avid readers of the local newspapers, and almost all participants in our pilot work were recruited from newspaper advertisements. Given the excellent response of older adults to participate in our pilot clinical trial, we expect that about one out of every four adults who self-identifies as having back pain will be eligible to participate, and that recruitment will last approximately 30 months.

Potential exclusions will be examined in two phases–the first phase will be 1) over the telephone using a structured questionnaire administered by a trained research assistant, or 2) in person at the General Internal Medicine Clinic by a trained research recruiter. Phase 2 of screening will be on-site at the University of Pittsburgh CRHC after individuals have signed informed consent in accordance with the University of Pittsburgh Institutional Review Board guidelines. The inclusion/exclusion criteria will be confirmed and the Folstein Mini-Mental Status Exam (MMSE) administered. If during the conduct of the on-site screening the MMSE reveals a clinically significant result (score < 24), permission to notify the participant's physician will be obtained. Study participants will also undergo a brief physical exam by a physician.

Permission to screen. All individuals who respond to the advertisement and recruitment strategies listed above will give their verbal consent to undergo telephone screening or in-person screening if consent is given on the tablet PC during the visit to the General Internal Medicine Clinic. The telephone screening will be performed by the research assistant using an IRB-approved script. A waiver of the requirement to obtain a signed informed consent document for telephone screening purposes will be requested since obtaining this information presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. The research assistant will document in the participant's chart that they have obtained verbal permission to ask the screening questions. Interested/eligible persons will be given a detailed description of study procedures before coming to the study site in order for them to determine if they wish to participate. On-site participants will be screened using the Folstein MMSE and the inclusion/exclusion criteria verified after they have given informed consent. A brief physical exam will be performed on all participants after they have signed informed consent. The goal of the exam is to identify red flags that could mean serious underlying illness that requires specialized medical attention and that would prevent participation in the study. If a condition is identified, written permission will be requested from the participant to contact their physician by telephone and report the findings to them. We realize a small number of participants may fail the MMSE or do no meet inclusion criteria after giving informed consent and will have to be excluded from study participation.

Permission to enroll in the study. After completing the screening procedure, subjects who qualify will be invited to come to the University of Pittsburgh CRHC. Each individual interested in participating in the study will receive a thorough explanation of the study (procedures, risks, benefits, participant rights) through the informed consent process prior to participating in any procedures (including prior to the screening MMSE and confirmation of eligibility). The PI or trained research assistant will review the consent document with each person and will insure that any questions are satisfactorily explained and that the person willingly agrees to participate in the

study. The PI and participants will sign and date the consent document; the original documents will be kept in locked files, and each participant will receive a copy. Participants will also be informed that they can withdraw at any time from the study if they choose. No coercion or social pressure will be exerted to participate.

Physical exam. During phase two of recruitment and after participants have signed informed consent, they will undergo a complete, structured physical exam by a physician. The goal of the exam is to identify red flags that could mean serious underlying illness or serious back conditions that require specialized medical attention and that would prevent participation in the study. We have developed a detailed musculoskeletal exam that is pain specific and systematically examines the areas of the body that contribute to low back pain. We will use this form during each participant assessment.[65] If a condition is identified, written permission will be requested from the participant to contact their physician by telephone and report the findings to them. In our experience in clinical trials with older adults, our exclusion criteria and medical exam accurately identifies those older adults with serious back conditions who should not participate in a clinical trial for their own safety.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration and Handling of Study Interventions

Study interventions: mind-body program
Frequency and setting: Participants will be seen in a group format once a week for 90 minutes for 8-weeks. Group size will be 10 participants per class. We found this to be the optimal class size in our pilot work because the group was small enough to encourage individual participation, but not too large that participants were afraid to talk.

The intervention will be modeled on the Mindfulness-Based Stress Reduction program (MBSR). All sessions will be led by either Daniel Schenck or Carol Greco. Each has experience in teaching the MBSR program to older adults with chronic pain. Each has undergone teacher training in at least one intensive ($\geq$ 50 hours) teacher training program conducted by the University of Massachusetts Medical School Center for Mindfulness. Daniel Schenck has practiced mindfulness meditation for 25 years and Carol Greco has practiced it for 14 years. All sessions will occur at the University of Pittsburgh CRHC, which has a large classroom, nearby parking, and is easily accessible by public transportation. Seniors may ride the public bus system for free in Pittsburgh.

Program Principles. The intervention is modeled on the work of Jon Kabat-Zinn at the Massachusetts Medical Center. He has adapted Eastern methods of mindfulness meditation to a Western audience. Four methods of mindfulness meditation will be taught. These techniques take regular activities like sitting, walking and lying down and transform them into a meditation through directed breathing and mindful awareness of thoughts and sensations.

The methods used are: 1) the body scan, where in a lying position, the participant is guided to place their attention non-judgmentally on each area of the body from the toes to the top of the head and directing the breath to each region in turn, 2) sitting practice, which is focused attention on breathing while sitting on a chair, 3) walking meditation, which is mindful slow walking with

focused attention on body sensation and /or breathing[18], and 4) mindful stretching: participants are taught to purposefully direct their awareness to physical sensation while doing simple stretching exercises while seated. In the original Mindfulness-Based Stress Reduction program the mindful movement component is yoga and in our modified program it is stretching. We did this change explicitly, taking into account that yoga may not be feasible for some older adults. We have recently piloted this and it was well-received and well tolerated.

Program Protocol. We found the 8-week mind-body program feasible in older adults with chronic pain. Participants were enthusiastic about the program, attended most of the classes, and adhered to the daily meditation homework assignments. Because of the positive feedback we received we will follow the same format in the proposed research study. A detailed class manual will be created at the beginning of the study that will allow it to be disseminated and distributed to those who want to replicate our methods. The core of the program is modeled on the MBSR Program, which has been described in detail.[18] The manual will be an expansion of the protocol we used in our pilot work and will contain the modifications that we have made to the program that address pain-specific topics. The 10 Keys™ program already has a detailed manual.

During the **first week** participants will be introduced to the principles and practice of mindfulness meditation. The homework requirement of daily meditation (six of seven days/week) lasting 50 minutes (45 minutes of meditation, 5 minutes to complete a log) will be reviewed. Support materials of CD recording, daily log and reading materials will be handed out. The CD recording is a 45 minute recording of the steps in the body scan meditation and a 30 minute recording of the sitting meditation that guides participants in meditation. Participants will be provided with a CD player if they do not own one. We expect about 1/3 of participants not to own CD players based on our experience with the pilot study. The reading materials will be reviewed during the sessions and are not part of the homework. The body scan technique will be taught at the first session. The group will meditate together using the body scan technique for 45 minutes at the first, second and eighth session. If physical discomfort should arise during any meditation participants will be encouraged to change to a more comfortable position. There is not a minimum amount of time required to stay in one position. The first class introduces mindful eating, which is done through a guided exercise of eating a raisin. This exercise begins to introduce the concept of informal meditation, in that mindfulness can be brought to everyday activities like eating.

There will be gentle stretching exercises introduced at the first class which will be chair-based (e.g., mindful stretching). The exercises will last for 20-30 minutes and will occur with every session. Participants will be taught how to bring mindfulness to body work and greater awareness of their body's response to gentle stretching. This will be reinforced by stressing that the exercises should be done slowly and synchronized with breathing.

The 8-week mind-body program

Week 1	Week 2	Week 3	Week 4
• Body scan • Raisin exercise • Mindful stretching	• Body scan • Sitting meditation • Stretching • Discussion: experience with meditation, this will be a component of all sessions. Mind-body medicine and the connection to pain will be discussed	• Sitting meditation • Mindful stretching • Discussion: the pain model (emotional, cognitive,sensory), the awareness of thoughts, sensations, and emotions during meditation and the relationship between the two	• Sitting meditation • Mindful stretching • Discussion: the flight/fight response, the relaxation response, and their relationship to pain
Week 5	**Week 6**	**Week 7**	**Week 8**
• Sitting meditation • Mindful stretching • Introduce walking meditation • Discussion: applying mindfulness to work with pain, this will be a component of all remaining sessions	• Sitting meditation • Mindful stretching • Walking meditation • Discussion: applying mindfulness to everyday situations	• Sitting meditation • Mindful stretching • Walking meditation • Discussion: awareness of thoughts, sensations, and emotions around pain, and breaking through habitual tendencies in reacting to pain	• Body scan • Mindful stretching • Discussion: synthesize what has been learned in the last 8-weeks.

During the **second** and following weeks the sessions will include a general discussion of the participants' experience with the meditation method, including problem-solving regarding obstacles to the meditation practice. Theoretical material related to meditation, relaxation, pain and the mind-body connection will be presented at this time. About 30 minutes will be spent at each session in these discussions. Also during the second week, quiet sitting meditation will be introduced. The group will practice together using the sitting meditation technique for 15 minutes during this and at the beginning of subsequent sessions.

The **third** session will introduce pain theory and the multidimensional response to pain. Participants will learn about the cognitive, emotional, and sensory components of nociceptive processing. The triangle of awareness will also be introduced, which describes the thoughts, emotions, and sensations that make up the activity that arises at any given moment in the mind. The relationship between the multidimensional model of pain and the triangle of awareness will be discussed.
The **fourth** session will introduce the flight or fight response and the relaxation response. This is an interactive session with participants describing their response to stress as well as their response to mindfulness meditation. Stress and the relaxation response will be discussed in relation to worsening or decreasing pain.

At the **fifth** week's session, walking meditation will be introduced. How to use mindfulness meditation methods to work with pain will be discussed. This will occur at this and all remaining sessions. An interactive approach will be taken, so that participants will discuss how they have used mindfulness meditation methods to work with pain. Participants will also be taught how to work with pain during formal meditation. They will learn this by guided meditation during this and subsequent sessions, as well as a recording on CD of the body scan that is specific for working with pain.

At the **sixth** week's session applying mindfulness to everyday situations (informal meditation) will be discussed.

At the **seventh** week's session breaking through habitual tendencies to coping with pain will be discussed.

The **eighth** session will integrate what has been learned over the course of the program.

Therefore, the structure of each session will be one hour (total) of meditation and 30 minutes of discussion.

Booster sessions. We expect that it will take more time than 8-weeks for participants to develop familiarity and proficiency with mindfulness meditation, as the program in and of itself is only an introduction to meditation. Research studies support this, showing an effect 6-12 months after completion of the program. Therefore, to encourage proficiency with the meditation method, we will have booster sessions. These will occur monthly and will last for one hour. Each session will be structured around 30-40 minutes of mindfulness meditation and 20-30 minutes of discussion around the themes brought up during the 8-week program.

The health education control program. A convincing comparison group is essential for participant recruitment and retention as well as essential to control for key components of the mind-body program. Therefore, the comparison group will control for time, group size, attention, homework, and facilitator time. We are basing the 8-week health education program on a successful aging curriculum known as the 10 Keys™ to Healthy Aging. Because this intervention teaches important health topics that are relevant to the older adult, it will provide a valuable program to participants. Pain information is not a component of the 10 Keys™ program, and we will not add this information to avoid contamination of the control group.

10 Keys™ to Healthy Aging

Key #1: Blood Pressure
Key #2: Smoking
Key #3: Cancer Screening
Key #4: Immunization
Key #5: Blood Glucose
Key #6: LDL Cholesterol
Key #7: Physical Activity
Key #8: Bone Loss & Muscle Weakness
Key #9: Social Contact
Key #10: Depression

The 10 Keys™ to Healthy Aging is an innovative community health outreach program developed by the Center for Healthy Aging (CHA) at the University of Pittsburgh. The CHA is a member of the Prevention Research Centers Program and is supported by the Centers for Disease Control and Prevention (www.healthyaging.pitt.edu). It teaches an interactive, dynamic program to older adults on "key" health topics relevant to healthy aging. It was first piloted in Pittsburgh in the fall of 2005. The first class was conducted in January of 2006. There have been 37 classes taught. A total of 478 older adults have enrolled in the program and 406 have completed it, for a retention rate of 85%.

There are 10 specific, targeted components in the program which are listed in the table. Each key provides important risk/benefit information related to the topic, tips about nutrition-related factors (e.g., reading labels to reduce sodium and fats), and homework assignments that ask participants to apply what they have learned in class. The curriculum also informs older adults about risk factors for diseases, such as hypertension, diabetes, and hyperlipidemia, and preventive strategies for improving health, including exercise, cancer screening, immunizations and social participation. Through this training program on healthy aging, participating members can become certified as Community Health Ambassadors. As training program completers, they are strongly encouraged to share this information with members of their social network (such as family and friends). The program will be taught by a health-educator who has trained as a Heath Ambassador. Kathy Williams, MHSA, RN, who is director of the Community Health Ambassador program at the Center for Healthy Aging, will serve as a liaison and suggest modifications to the 10 Keys™ program so that it will be made up of 8-weekly sessions instead of the 6-weekly sessions typically offered to the community. A detailed class manual is available and materials that have been developed for the 10 Keys™ program will be used.
Efficacy data is available on 89 adults who have gone through the 10 Keys™ program and become themselves Community Health Ambassadors (enabling them to teach the program in the community). Health Assessments were completed at baseline and 12 month follow-up assessing adherence to the 10 Keys™ to Healthy Aging goals. There were 89 older adults who completed the program (79 % women, mean age 72, 98% white). Over half were married (55%), with 98% completing high school or greater. One year after completing the program, the proportion with LDL cholesterol less that 100 mg/dl increased from 28% to 38% (P=0.029). For colonoscopy,

rates increased from 74% to 81% (*P*=0.014).

Booster sessions. To ensure the control group receives an equal amount of attention and social support, we will also offer monthly booster classes to them. They will meet, like the intervention group, monthly, for one hour. The classes will be based on the topics presented in the 10 Keys™ to Healthy Aging. During the 10 Keys™ program each participant is encouraged to set personal goals and action steps toward meeting those goals as well as complete homework assignments around the topic for each class. For example, Key 7 involves education on exercise, encourages setting exercise goals, listing steps toward reaching those goals, and discussing with a physician. The booster will comprise a refresher of one of the 10 Keys™, review whether goals were met and homework assignments reinforced.

5.2 Adherence Assessment

Assessment and monitoring. The mind-body group will be provided with logs for recording meditation sessions at home. The logs will include sections to record the date and time in minutes of a meditation session, any problems or benefits of the session as well as perceived quality of the meditation experience on a simple 0 (poor) to 10 (excellent) scale. Logs will be collected weekly. Both the intervention and control group will have attendance at group sessions recorded.

Interventions to promote adherence and retention. Adherence-promoting strategies for the mind-body group for home meditation includes the log, audio recording and instructional materials. Group sessions will stress the importance of home practice and group participation, and discussion will include problem-solving around barriers to the meditation practice. Attendance at the weekly sessions will be encouraged by free parking and/or cab fare (provided through vouchers). The control group will also have attendance taken at each session, will be reminded of the importance of group participation and how to implement what they have learned during each class for their own health, and will also be encouraged to attend by availability of free parking and/or cab fare.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Timetable of Measures

Measure	Baseline	8-Weeks	6 & 12-Months	Monthly
Physical Function				
Roland Disability Questionnaire: **primary outcome measure**	X	X	X	X
SF-36 Physical Function Scale	X	X	X	
Short Physical Performance Battery	X	X	X	
Repetitive Trunk Rotation	X	X	X	
Pain				
McGill Pain Questionnaire	X	X	X	
Pain Numeric Rating Scale (0-20)	X	X	X	X
Multidimensional Pain Inventory	X	X	X	
Neuropsychological Performance				
Computer-Based Assessment of Mild Cognitive Impairment	X	X	X	
Psychological Function				
SF-36	X	X	X	
Chronic Pain Acceptance Questionnaire	X	X	X	
Geriatric Depression Scale	X	X	X	
Generalized Anxiety Disorder-7	X	X	X	
Chronic Pain Self Efficacy Scale	X	X	X	
CSQ Catastrophizing Scale	X	X	X	
Fear Avoidance and Beliefs Questionnaire-Scale 2	X	X	X	
Profile of Mood States	X	X	X	
Social Support	X	X	X	
Mindfulness				
Five Facet Mindfulness Questionnaire	X	X	X	
Mindful Attention Awareness Scale (5 & 15 item)	X	X	X	X (5-item only)
Other				
Cumulative Illness Rating Scale	X			
Medications	X	**X**	**X**	**X**
Health System Encounters		X	X	X
Physical Activity Scale	X	X	X	
Treatment Credibility and Expectancy Ratings	X	X	X	
Patient Global Impression of Change		X	X	

6.2 Description of Evaluations

Outcome measures

Outcome measures were chosen to reflect our primary aim of determining the impact of the mind-body program on physical function, pain, and psychological function. Outcome measures were also chosen because of their demonstrated feasibility, reliability, and validity in older adults with chronic pain. All 300 participants who are included based upon the screening criteria outlined above will receive identical pre-treatment baseline assessments. Data will be collected and interviewer-administered by a trained research assistant at the University of Pittsburgh CRHC who is blinded to group assignment. We will use a paperless data management system. We have carefully chosen measures that are quick to administer and complete. In our experience, almost all the individual measures can be done in 5 minutes or less and many of them in even less time because they have so few questions (as few as four). Therefore, the estimates of time to complete the measures that we present below are based on our experience with older adults.

Measures of physical function. Physical function will be assessed using self-report measures, as well as performance-based measures because of the different strengths of these two approaches. Self-report measures tap into the subject's perceived abilities and are time and economically efficient, but can be influenced by respondent reporting bias.[67] On the other hand, performance measures assess various aspects of functioning that cannot be detected in a questionnaire and may increase our knowledge about the degree to which pain influences function.[68] Other investigators have demonstrated that self-reported and observed measures of physical function appear to tap different constructs. **Performance-based measures** were carefully selected to reflect movements that are closely related to everyday activities, thus increasing their ecological

validity. The measures assess everyday movements that produce mechanical stress on the lumbosacral spine and measure functional limitation.

(a) ***Roland and Morris Disability Questionnaire (RMDQ).***[69] ***This will be our primary outcome measure***. It contains 24 questions related specifically to functional limitations as a result of low back pain such as "I change position frequently to try and get my back comfortable" or "Because of my back, I use a hand rail to get upstairs." A score of 0 means there is no disability due to the back, and a score of 24 means there is severe disability. Normative data have been published for older adults with chronic pain to aid in the interpretation of the RMDQ scores. Mean scores for older adults were around 12.[70] Because of this, we have chosen a cut-off score of 12 to be eligible for the study. The RMDQ has been shown to be reliable and valid in community dwelling older adults with CLBP.[71] Internal consistency ranges from 0.87-0.95.[72,73] A clinically meaningful change on the RMDQ ranges from a 2.5 to a 5 point improvement.[74-77] Because this change has been determined in a younger back pain population and not in older adults, we have chosen the lower end of the clinically meaningful change in our hypothesis, as one would expect older adults to be less resilient to change due to natural affects of aging on the musculoskeletal system (e.g., joints).

(b) ***Short Physical Performance Battery (SPPB)*** [78-80] tests lower extremity function by measuring standing balance, gait speed and timed chair rise, tasks that are commonly encountered by older adults. It has been subjected to rigorous psychometric evaluation in numerous populations of older adults. It predicts both risk of disability as well as mortality.[79] ***Repetitive Trunk Rotation,*** a timed assessment of 25 rotations that measures spinal mobility and endurance (e.g., axial function) will be administered in both the standing and sitting positions. Trunk rotation without load is encountered throughout routine activities of daily living, such as retrieving objects from drawers or cabinets, dressing, and reaching items while seated in a car.[81] It has strong discriminant validity for CLBP as compared to pain-free older adults.[82]

Measures of Pain. The *Numeric Pain Rating Scale (NRS)*[83] is commonly used to measure pain. A score of 0 represents "no pain" and 20 represents "pain as bad as it could be." The 0-20 NRS is a preferred pain measure among older adults and has been found to be sensitive to changes in pain sensation in this population.[84,85] ***McGill Pain Questionnaire-Short Form (MPQ-SF)***[86] is a widely used, validated and reliable generic pain measure that has been used in an older population. Pain is measured in three domains: sensory, affective and total descriptors. We are adding this second measure of pain as it includes an affective dimension.

Measures of Neuropsychological Performance (NP). Based on our preliminary research, the executive function and attention domains of NP are most likely to mediate improvement in physical function. These domains of NP belong in the cognitive domain in our model of pain processing and mindfulness meditation.

To assess general intelligence we will use the well-established ***National Adult Reading Test (NART).***[87] For NP we will use the ***Computer-Based Assessment of Mild Cognitive Impairment (CAMCI).***[58,59] The CAMCI collects data in a standardized fashion and resembles a simple screening test that is user-friendly to the older adult. The CAMCI is presented on a tablet PC with touch screen response and takes approximately 30 minutes to complete. The CAMCI

includes an assessment of executive function and attention described in detail below**.** The grouping of selected tests was based on conceptual grounds and in consultation with expert neuropsychologists, all with more than 25 years experience in clinical assessment. Even persons with minimal or no computer background are able to easily complete the CAMCI – over 1200 adults have successfully used the CAMCI with less than a .5% failure rate.

CAMCI:

Measures of the Executive Function Domain: 1) ***Part 2 of the Tracking Test,*** for this test the computer displays a series of numbers and months in circles and participants are asked to connect the circles on the screen alternating between months forward, January through December, and numbers in reverse order, 12 to 1. The test is scored for number correct and time taken to completion. We chose this test as our primary outcome measure for Specific Aim 2 because it is a measure of executive function very similar to the measure used in the preliminary work presented in C.6 and which we found mediated the relationship between pain and physical function.

2) ***Go/no go task,*** where participants are asked to tap the screen twice if they hear one beep and once if they hear two beeps. The rules are then changed and they are asked to tap twice if they hear one beep and do nothing if they hear two beeps. Scores range from 0 to 10 with lower scores indicating poorer executive function.

3) ***Reverse digit span,*** participants hear a series of numbers and are then asked to tap numbers on a display on the bottom of the computer screen in the reverse order. The longest series with at least one correct is the obtained score.

4) ***ATM transaction,*** where participants are shown an ATM-type screen and asked to make a transfer of funds from saving to checking. Number of correct transactions and time are recorded.

Measures of the Attention Domain: 1) ***Part 1 of the Tracking Test,*** for this test the computer displays numbers 1 through 22 in circles and the participant is asked to connect the string of 22 numbers in ascending order by taping on the screen. The score is number correct out of 22 and the time taken to completion. This test is very similar to the Trails A test presented in C.7 and which was found to be significantly improved at program completion.

2) S*tar task,* where respondents are instructed to respond to an infrequently occurring stimulus. Scores are number correct out of 16 targets and median reaction time for correct and incorrect responses.

3) ***Digit forward span,*** participants hear a series of numbers, one per second, and after presentation are asked to tap the numbers in the same order on a number display (1 through 9) presented on the bottom of the computer screen. The longest series with at least one correct is the obtained score.

Measures of Psychological and Social Function. Because pain is a complex phenomenon that affects quality of life, mood, and psychological function we have chosen a variety of established instruments to measure these different domains. We have piloted all these measures on older adults, and none take more than 5 minutes each to administer, and many take much less time because they have less than 10 questions.

1) Quality of life will be measured with the ***SF-36 Health Survey*****.**[88] The two summary scores (physical and mental health) and eight scale scores will be measured. Normative data is available for older adults.
2) Given the strong association between chronic pain and depression,[89] the ***Geriatric***

Depression Scale[90] will be employed.

3) The ***Chronic Pain Acceptance Questionnaire***[91,92] is a 20-item scale that measures acceptance of pain which has been shown to correlate with reports of lower pain intensity and less physical disability.
4) Life control, affective distress, pain intensity, and pain interference with daily activities will be measured with the first section of the ***Multidimensional Pain Inventory.***[93]
5) Coping: An important contributor to disability in younger chronic pain sufferers, this construct is starting to be explored in older adults. We will explore this issue using the ***Catastrophizing Scale of the Cognitive Strategies Questionnaire.***[94]
6) Fear of Movement: The ***Fear-Avoidance Beliefs Questionnaire***,[95] validated in chronic lower back pain, predicts self-reported disability in older adults.[96]
7) Self-efficacy has been shown to predict task performance.[97] We will measure this construct with the well-validated ***Chronic Pain Self-Efficacy Scale.***[98]

Maximum time for completion of baseline, post-treatment, and 6/12 month measures	
Physical function and pain	30 minutes
Psychological function	30 minutes
Neuropsychological performance (CAMCI)	30 minutes
Mindfulness	10 minutes
Total time	100 minutes

8) Mood will be assessed with the ***Profile of Mood States (POMS).***[99] It reports on six subscales of mood: tension, depression, anger, vigor, fatigue, confusion, and a total mood score.
9) Anxiety is associated with chronic pain.[100] We will assess it with the 7-item scale ***Generalized Anxiety Disorder-7 (GAD-7).***[101] It has been shown to be valid among primary care patients.
10) The extent of social support may affect an individual's response to the mind-body or control program. This will be measured with the ***REACH (Resources for Enhancing Alzheimer's Caregiver Health) Social Support Scale.*** It assesses four areas of support: received support, satisfaction with support, social network, and negative interactions. It has good psychometric properties.[102-105]

Measures of Mindfulness

Mindfulness; which is key to the meditation method, remains unexplored in an older population. We will explore it with the ***Five Facet Mindfulness Questionnaire*** [106] which separates mindfulness into five domains: observing, describing, acting with awareness, nonjudging of inner experience, and nonreactivity to inner experience. We will also assess mindfulness with the ***Mindful Attention Awareness Scale (MAAS)*** [107,108] which measures attention and awareness of present moment experience in daily life. There is a 15 item and 5 item version.

Additional Baseline Variables

1) Demographic factors: will include age, gender, ethnicity, socioeconomic status, and marital and educational status.
2) Biomedical factors:

(a) Medications – Since number of medications has been shown to correlate with functional status in older adults,[109] all prescription and over-the-counter medications currently used will be recorded. We will track this at baseline, monthly during the course of the intervention, and monthly during the 12-month follow-up period. Participants will receive a phone call that will review with them their current medication list (obtained at baseline) and ask them to update it with any new or discontinued medications. Participants will be given a medication diary to record any over the counter and prescription pain medicine taken during the month,

and then this will also be reviewed with them during the monthly phone call. The medication data will be directly input into an electronic form during the baseline assessment and during the monthly phone calls. Comorbidity – It has previously been suggested that the number of medical diagnoses unrelated to pain contribute independently to compromised functional status in older adults.[110] Thus, data on comorbidity will be gathered using the Cumulative Illness Rating Scale.[111]

(b) Health System Encounters – Since unexpected acute illness/injury, comorbidity exacerbation or other pain treatments may affect response to measures, this will be assessed with simple yes/no questions and if answered positively, a description of the event. We will track this at baseline, monthly during the course of the intervention, and monthly during the 12-month follow-up period. We will ask participants about hospitalizations, visit to an emergency department, visit to a physician's office, as well as other therapies for pain control including physical therapy, injections and complementary therapy use such as chiropractic, acupuncture and yoga in the past month.

(c) Self-rated heath (SRH): Given the strong association between SRH and morbidity/mortality and pain intensity in older adults,[112-114] this will be measured using question 1 of the SF-36.

(d) Interim changes in physical activity level: will be determined with the Physical Activity Scale for Individuals with Physical Disabilities.[115] This brief 13-item instrument is a modified version of the valid and reliable Physical Activity Scale for the Elderly.[116,117]

(f) Treatment expectancy: will be collected to assess if participants perceived the two programs to be of equal face validity. Questions will include subjects' rating of their level of confidence with the treatment, whether they would recommend the treatment to a friend, perceived expertness of the treating clinicians, and expectation of positive treatment outcomes. Participants will also be asked to evaluate their global impression of change at the conclusion of the 8-week program, and at 6 and 12 months follow-up.

The anticipated time to complete the measures is 100 minutes. Our experience in running clinical trials in older adults is that they tolerate this amount of evaluation without experiencing undue fatigue or burden.

Monthly evaluation of treatment outcome. To examine the process of change, brief (15 minutes) monthly telephone evaluations of major important domains (function, pain, mindfulness, health system encounters, medication change, other therapies for pain such as medications, injections, or complementary therapy like chiropractic, acupuncture or yoga) will be conducted for all participants. The measures are a subset of the collected baseline measures (see Timetable of Measures). These data will allow a detailed examination of the temporal association of the individual months of the mind-body and control program with the primary outcome of physical function as well as secondary outcomes of pain, psychosocial function and neuropsychological performance. It will also allow a detailed examination of the temporal relationship between time and frequency meditating and the primary and secondary outcomes. All measures will be collected monthly over the telephone. These measures will be collected by the research assistant who will be blinded to randomization assignment.

Qualitative evaluation. The mind-body method of mindfulness meditation has not been studied in older adults with chronic pain outside of our pilot work. In our qualitative study of participants in the mind-body program, we found results were heterogeneous among participants, such as

descriptions not only of pain reduction, but improvement in sleep and physical and emotional well-being. This was not unexpected given the multi-dimensional approach to pain of the mind-body program. However, there were descriptions of the life-changing effects of the mindfulness method that go beyond what is described in traditional pain theory. This leads us to believe that there may be more domains that mindfulness affects in older adults that cannot be adequately captured with quantitative measures.

Focus Groups. We will conduct focus groups with the intention to collect detailed personal accounts of the experience of learning mindfulness and its associated affects. We will ask all participants who have completed the mind-body program and 6-month measures to participate in focus groups. This will be presented during the original informed consent process. Focus groups will continue on an on-going basis until theme saturation has occurred. This means that no further themes are brought up by participants and is used in qualitative research to indicate complete exploration of a topic. We anticipate carrying out approximately 6 focus groups. Each group will consist of approximately 10 participants. Participants with be reimbursed $75 for their time. The script will be developed during year 2 of the study and will include open-ended questions to stimulate conversation. This approach will also allow us to ask questions that can directly assess a variety of outcomes such as function and pain and life transformation. We will be able to explore more directly statements that deserve more explanation, such as describing an ability to "concentrate" better, or when participants describe their life having changed.

A trained focus group moderator will conduct the focus group sessions. Each session will last approximately 90 minutes. The sessions will be audio-recorded and transcribed. An approach based on grounded theory will be used to analyze the transcripts. Grounded theory in qualitative research is a powerful analytic approach that refers to theory that is inductively generated from the researcher's observations and not deduced from the laboratory bench.[118] With this approach, the data will be amassed and examined using content analysis to identify recurring words, phrases or concepts. These will then be assigned codes. Key themes detected will be based on the codes that emerge from the data. We will import the transcripts into the qualitative software package ATLAS.ti 5.0 (ATLAS.ti Scientific Software Development, Berlin, Germany) to facilitate the coding process.

7. SAFETY ASSESSMENTS

Potential Risks. Minimal risks to participants are anticipated. Potential increased pain may result from sitting on a chair during sitting meditation. However, participants will be taught how to mindfully change their posture if worsened back pain should occur. All subjects will be told that they are free to withdraw from the study at any time and will be told of any potential risk prior to participating in the study. Furthermore, focus group participants may feel uncomfortable talking in front of others. We will minimize this risk by reminding participants of their ability to withdraw from the study prior to the focus groups. Breach of confidentiality is always a risk-however remote.

Protection Against Risks. All subjects will be told that they are free to withdraw from the study at any time and will be informed of any potential risks prior to their participating in any study procedures. The risk of breaching subject confidentiality will be minimized by identifying all participants by code numbers and by securing all data collected in locked files in areas accessible

only to research personnel. All databases will be password protected.

The participant may experience increased discomfort in their back from sitting on a chair during sitting meditation. However, they will be taught how to mindfully change their posture if worsened back pain should occur.

There is a rare risk (less than 1 out of 100 people) that during the physical testing procedure the participant could fall when they are asked to walk 4 meters (about 12 feet) or when their balance is being tested. However, Dr. Natalia Morone or a trained research assistant will be present during all tasks and help steady the participant if need be. This will help minimize the risk of falling. There is a risk of feeling uncomfortable talking in front of others while participating in the focus groups. We will minimize this risk by reminding participants that the focus groups are voluntary. Finally, there is a risk of breach of confidentiality. The risk will be minimized by the use of study IDs in place of participant names on all study related materials.

Potential Benefits. Participants in the mind-body group may increase physical function and experience a reduction of pain as well as improved quality of life. Individuals in the education control group will have had the opportunity to learn about healthy behaviors and strategies to optimize their health while aging. There is also the development of an adjunctive nonpharmacologic, noninvasive and safe treatment for older adults with chronic low back pain.

Importance of the Knowledge to be Gained. Chronic low back pain is a prevalent and potentially devastating problem for older adults, both from the standpoint of function, pain and quality of life. Traditional treatment modalities (medications and surgery) are often associated with significant risks, thus the development of safe, alternative treatment that will help to promote the independence of community dwellers is essential. We believe that mindfulness meditation represents a safe and feasible treatment option that ultimately will lead to decreased pain, improved physical and psychosocial function, and decreased utilization of health care resources.

7.1 Adverse Events and Serious Adverse Events

For determining severity we use the following definitions (below). If a participant has an emergency department visit (but not hospitalized and discharged to home), then they are assigned of moderate intensity and if the participant is hospitalized it is assigned of serious intensity.

Adverse Event: Any untoward medical occurrence that may present itself during the conduct of a research study and which may or may not have a causal relationship with the study procedures.
Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.
Moderate or greater severity. This adverse event requires medical evaluation and/or medical treatment; or is a serious adverse reaction.
Serious. This adverse event is fatal or life-threatening; requires hospitalization; or produces a disability.

7.2 Reporting Procedures

All adverse events will be reported according to the following time line.

If the event is **fatal or life-threatening**, the report to the IRB and the DSMB will occur within 24 hours of the event.

If the event is **unexpected**, and of **moderate or greater severity** (but not fatal or life-threatening), and associated with the research intervention, shall be reported to the IRB and the DSMB within 10 calendar days of the reaction.

The IRB and the DSMB will also be notified as soon as possible of major disputes between the PI and/or project staff and a research subject or between research investigators (including research staff) involved in the proposed program of research if the resolution of the dispute is or will be problematic.

7.3 Safety Monitoring

Data and Safety Monitoring Board (DSMB) will be created because the proposed program of research will be performed on a frail population, i.e., adults > 65 with chronic pain. The DSMB will act in an advisory capacity to the National Institute on Aging (NIA) to monitor subject safety and evaluate the efficacy of the intervention.

The initial responsibility of the DSMB will be to approve the initiation of this clinical trial. After this approval and twice a year during the course of the trial, the DSMB responsibilities are to:

1. Review the research protocol, informed consent documents and plans for data and safety monitoring;
2. Evaluate the progress of the trial, including assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the trial site, and other factors that can affect study outcome;
3. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
4. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the PI;
5. Protect the safety of the study participants;
6. Report on the safety and progress of the trial;
7. Make recommendations to NIA and the PI concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
8. Ensure the confidentiality of the trial data and the results of monitoring;
9. Assist NIA by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

Membership. The DSMB will include experts in back pain treatment, the MBSR program, clinical trials methodology, and biostatistics. Members will consist of persons completely independent of the investigators who have no financial, scientific, or other conflict of interest with the trial. Current or past collaborators or associates of Dr. Morone will not be eligible to serve on the DSMB.

The University of Pittsburgh will provide the logistical management and support of the DSMB. A safety officer will be identified at the first meeting. This person will be the contact person for severe adverse event reporting. Procedures for this will be discussed at the first meeting.

Board Process. The first meeting will take place via teleconference before initiation of the trial to discuss the protocol, approve the commencement of the trial, and to establish guidelines to monitor the study. The PI will prepare the agenda to address the review of manual of operating procedures, initiation of the trial, identification of a safety officer, reporting of adverse events, etc.

Meetings of the DSMB will be held 2 times a year (via conference call) at the call of the Chair.

Meetings shall be closed to the public because discussions may address confidential patient data. Meetings will be attended by the principal investigator and members of her staff. An emergency meeting of the DSMB will be called at any time by the Chairperson should questions of patient safety arise.

Meeting Format. DSMB meetings will attended by the principal investigator, institution staff, and will always include the study data analyst. Issues discussed will include conduct and progress of the study, including patient accrual, compliance with protocol, and problems encountered. Patient-specific data and treatment group data may not be presented in the open session. Should the DSMB decide to issue a termination recommendation, full vote of the DSMB will be required. In the event of a split vote, majority vote will rule and a minority report will be appended.

Reports. Interim Reports. Interim reports will be prepared by the study data analyst and distributed to the DSMB at least 10 days prior to a scheduled meeting. These interim reports will be provided electronically. The contents of the report will be determined by the DSMB. Additions and other modifications to these reports may be directed by the DSMB on a one-time or continuing basis. Interim data reports will be an Open Session Report and will provide information on study aspects such as accrual, baseline characteristics, and other general information on study status.

Reports from the DSMB. A formal report from the Chair will be sent to the full DSMB within 3 weeks of the meeting. Once approved by the DSMB, the Chair will forward the approved minutes to NIA within 6 weeks of each meeting.

Each report will conclude with a recommendation to continue or to terminate the study. This recommendation will be made by formal majority vote. A termination recommendation may be made by the DSMB at any time by majority vote. The Chair will transmit such a

recommendation to NIA as rapidly as possible, by immediate telephone and telefax if sufficiently urgent. NIA will then notify the PI. In the event of a split vote in favor of continuation, a minority report will be contained within the regular DSMB report. The report will not include unmasked data, discussion of the unmasked data, etc.

Confidentiality. All materials, discussions and proceedings of the DSMB will be completely confidential. Members and other participants in DSMB meetings will be expected to maintain confidentiality.

8. INTERVENTION DISCONTINUATION

It is possible that participants may be removed from the research study by the researchers if, for example, they score 23 or less on the Mini Mental Status Exam. They may also be removed if they are found to have a serious illness or a back condition as a result of the physical exam.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size and Randomization

Sample Size. We propose to recruit a total of 300 participants (150 per intervention arm) to allow approximately 120 participants per intervention arm available for a complete case analysis (assuming 20% attrition). In trials such as ours that are randomized at the individual level but the intervention is delivered in the group setting, there is an anticipated correlation among the outcomes of individuals within the same groups. This violates the assumption of independence used in most statistical methods. A common measure of this correlation is the intraclass correlation coefficient (ρ). Importantly, if we ignore this correlation coefficient we risk being underpowered to detect a meaningful effect.[119] We have no preliminary data to estimate the intraclass correlation for participants within the same group so we have used estimates that have been cited in the literature for human studies. Power analysis was conducted in NCSS/PASS[120] using the cluster randomization algorithm for a two-sample t-test assuming 12-15 class cohort groups per intervention arm and 10 individuals per class. With α=0.05 using a two-sample t-test for clustered randomized trials, adjusted for correlation within groups (ρ=0.01-0.02; for human studies),[121] we have 80-90% power to detect a 2.5 point difference in the Roland and Morris Disability Questionnaire using an average standard deviation of 5.9 from our pilot work (effect size 2.5/5.9=0.42). We consider this difference of 2.5 to be a minimum value with respect to clinically significant improvement in function. This sample size is large enough to counter the valid criticism that mind-body studies are underpowered to assess their effects. We will also be able to capture other small effects that would be missed with a smaller sample size.

Randomization Procedure. After successful screening, written informed consent, physical exam, and baseline measures have been completed, all eligible research participants entering this study will be randomized into one of two groups 1) mind-body program (intervention) or 2) education group (control). The randomization process will be performed by the biostatistician using statistical software with a random-number generator to create a list of group assignments before study recruitment begins. Randomization will occur in blocks of 4. The assignments are created based on the specific number of expected eligible participants and divided equally between the intervention and control group. Once an eligible participant has been screened, has

signed informed consent, and has completed the baseline measures and physical exam, a research assistant or PI submits a request to randomize the eligible participant. The program locates the first unassigned record in the randomization list and assigns the participant to the group designated in that record. The participant identifier and date are written to the record. Only those not blinded to the group assignments have access to view the randomization table; this will include the PI, unblinded research staff, and data management staff. No one will be allowed access to the folder that determines randomization assignment until all baseline measures have been completed.

Modification to original randomization plan (March 2013): After 155 (52% of total targeted sample size) participants had been randomized, there was a significant imbalance between groups by gender. At 57% of the targeted randomization (N=300) with approval from the Data Safety Monitoring Board, we changed the fixed randomization to a baseline adaptive randomization to balance future allocations by gender.[66] The web-based data collection system was modified to randomize in real-time using the minimization method rather than the fixed list. Only after baseline measures were completed was the allocation available for access by the Project Coordinator who then communicated the assignment to the participant in-person or by phone. All outcome assessments were conducted by staff members blinded to intervention assignment.

9.2 Data Analyses

Treatment comparisons of primary and secondary outcomes.
Specific Aim 1: To determine the effectiveness of a mind-body program in increasing function and reducing pain among older adults with chronic low back pain.
Hypothesis 1: Mindfulness meditation will be associated with a clinically meaningful 2.5-point improvement in the Roland and Morris Disability Questionnaire, which is specific to the low back, immediately following an 8-week mind-body program as compared to an education control group.

To test whether the negative impact of pain on function can be reduced from mindfulness meditation, we will administer the Roland and Morris Disability Questionnaire immediately following completion of the 8-week intervention or control program. Previous analysis of data from our pilot study show the RMDQ scores to be normally distributed in this population of adults. We will compare average function at this time point using a mixed effects model with a fixed effect for intervention group and a random class effect. We are proposing to control for classes as a random effect because we hypothesize that responses immediately following each 8-week program will be correlated for participants that are in the same class. Dynamics specific to each class such as the participants themselves**,** questions and discussions may influence participants' functional statuses in the same manner for participants in the same class. Although we anticipate this correlation among participant responses to be small, we feel it is appropriate to control for this relatedness so that we do not falsely conclude the mind-body program is more effective than the control program. We have also taken this into account in our sample size planning. In an additional analysis for testing intervention effects on function, we will use an analysis of covariance (with random class effects) to control for baseline function[122,123] and important demographic and biomedical measures that were either imbalanced between the groups at baseline or that are predictive of function.

We will compare function across time (immediate post-treatment, 6 months post treatment, 12 months post treatment) using a mixed model with type of program serving as the between-subject factor and time of assessment the within-factor treated as a categorical variable. Subject and class will be treated as random effects to control for the correlation among repeated measurements on the same person and correlation among measurements of participants in the same class. We will test for a difference in the change in function over time using an interaction term between treatment group and time (immediate post treatment, 6 and 12 months). If this is non-significant, we will test the main effect of treatment.

Hypothesis 2: Compared to the control group, intervention participants will experience higher levels of functional status, decreased pain and increased psychological function immediately following the 8-week mind-body program.

The analysis for this hypothesis will focus on the other measures of functional status which are general (SF-36 Physical Function scale) and specific to lower extremity function and spinal mobility (SPPB and repetitive trunk rotation) immediately following the 8-week programs. We will use linear mixed models for each function measure with a fixed intervention effect and random effect for class controlling for baseline measure. We will also test the immediate intervention effects on measures of pain (NRS< MPQ-SF) and psychological function (nine continuous measures) using the same methodology. Each analysis will be conducted at α=0.05 since these measures are secondary to function as measured by the RMDQ.

Hypothesis 3: At 6 and 12 months follow-up, the magnitude of improvement in physical function, pain, and psychological function will be at least the same or improved since completion of the 8-week program.

The analysis for this hypothesis focuses on testing for long-term intervention effect on function, pain, and psychological function at 6 and 12 months. We propose to use linear mixed models for the pooled data on each outcome with fixed effects of intervention, time (immediate post treatment, 6 and 12 months), and their interaction controlling for the baseline measure. Subject and class will be treated as random effects to control for the correlation between repeated measurements on the same person and correlation among measurements of participants in the same classes. We do not anticipate a significant interaction but we do expect the mindfulness meditation group to have overall better measures across time (significant main effect for intervention).

Specific Aim 2: To evaluate the impact of mindfulness meditation on NP in older adults with chronic low back pain.

Hypothesis 1: Mindfulness meditation will be associated with a significant improvement in the Tracking Test, part 2 of executive function immediately following an 8-week mind-body program as compared to an education control group.

Our conceptual model suggests that improved cognition could alter the processing of a painful stimulus and potentially limit the impact of pain (this corresponds to the middle portion of the model that describes pain processing). We propose to measure this "top-down" regulation of pain

by measuring NP. The primary NP outcome we will study is executive function as measured by time taken to complete (in seconds) the Tracking Test Part 2, immediately following eight weeks of either program. This measure will be treated as continuous as has been done in previous studies.[124] We will test immediate effects (at program completion at eight weeks) on executive function using a mixed effects model with a fixed effect for intervention group and a random class effect (approximately 16 classes, 8 intervention and eight control) controlling for baseline executive function.

Hypothesis 2: Improvement in executive function and attention will be significantly associated with improved physical function immediately following an 8-week mind-body program.
We will first estimate simple correlations among changes in executive function and attention and physical function immediately following the 8-week program relative to baseline regardless of intervention group assignment. We will then use multiple linear regression models to test if improvement in executive function and attention are associated with improved physical function (relative to baseline). We will use regression diagnostics to assess model assumptions, detect potential outliers, and examine collinearity.

Hypothesis 3: Improvement in executive function and attention will mediate the relationship between pain and physical function.
An analysis that would complement our conceptual model would be a mediation analysis where we demonstrate that the effect of mindfulness meditation on physical function is partially mediated by cognitive function (one of the three domains in the model that is involved in processing a nociceptive stimulus). There are three major approaches to mediation analysis, 1) causal steps,[125] 2) difference in coefficients, and 3) product of coefficients.[126] There are several limitations to the causal steps approach such as low power to detect mediated effects and requirement that the treatment be significantly related to the outcome (physical function). Therefore, we proposed to use single-mediator and multiple mediator methods incorporating product of coefficients as described by MacKinnon, Fairchild, and Fritz to test for mediation.[127] For the simple single-mediator analysis, we first must demonstrate that the meditation program has a significant effect on executive function (mediator) immediately after the programs at 8 weeks using a linear mixed model controlling for random class effects. We then will test if immediate post-intervention physical function (as measured by the RMDQ) is correlated with executive function (mediator, Part 2 of the Tracking Test). Both tests would have to be significant for there to be evidence of mediation. We will estimate the mediated effect by taking the product of the following coefficients: 1) the coefficient for the intervention effect on executive function, 2) the coefficient for executive function in a model testing the intervention effect on physical function controlling for executive function. This estimate will provide the reduction in the program effect on physical function when adjusted for neuropsychological function. The confidence interval for the mediated effect will be calculated using bootstrap methods. If zero is not contained in the interval, then we would conclude significant mediation exits.[128] Since our mindfulness meditation program targets multiple cognitive pain processing mechanisms, we will test for a multiple-mediator model using executive function and attention.

Hypothesis 4: At 6 and 12 months follow-up, the magnitude of improvement in neuropsychological performance and physical function will be at least the same or improved since completion of the 8-week program.

To compare treatment groups, the same analysis as proposed in Aim 1, Hypothesis 3 will be conducted. The analysis for this hypothesis focuses on testing for long-term intervention effects on executive function and attention at 6 and 12 months. We propose to use linear mixed models for the pooled data on each outcome with fixed effects of intervention, time (immediate post treatment, 6 and 12 months) and their interaction controlling for the baseline measure. Subject and class will be treated as random effects to control for the correlation between repeated measurements on the same person and correlation among measurements of participants in the same classes. We will test for a difference in the change in executive function over time using an interaction term between treatment group and time. If this in non-significant, we will test the main effect for intervention group. We do not anticipate a significant interaction but we do expect the mindfulness meditation group to have overall better measures across time (significant main effect for intervention group).

Additional Analyses

Pain medication. Pain medications will be monitored on a monthly basis in addition to utilization of physical therapy, injections, chiropractic manipulation, acupuncture or yoga. The differential use of these concomitant therapies could bias our results with respect to the intervention effects if two criteria are met: 1) utilization is highly prevalent, and 2) therapies are effective in reducing pain. We will conduct several analyses to investigate the potential impact that the utilization of these therapies may have on our intervention program comparisons. We will first compare the prevalence and patterns of utilization across intervention groups. We will then test if the persons using these therapies have better pain relief and function over time as compared to persons that do not use these therapies. If both criteria above are met, we will conduct a sensitivity analysis for the mind-body program comparisons at 8 weeks, 6 months, and 12 months that will first subset to only persons that did not use or had very low use of additional therapies and estimate the mind-body intervention effect. Then we will add in persons with moderate concomitant utilization and then persons with higher utilization so that we can completely address the impact on the mind-body program effect. Our experience in previous clinical trials[129] showed that very few participants chose to use additional therapies. Of 200 participants over the course of the 6-month trial, a total of 6 used physical therapy, 7 chiropractic, 3 injection therapy and there was no significant change in pain medication use.

Subgroup analyses. We will conduct analyses in an exploratory fashion to check for consistency in intervention effects across potentially moderating variables. Variables to be considered are age, sex, race/ethnicity, education, and IQ. Continuous variables will be categorized at their respective medians. We will first stratify the analysis by subgroup (example: males and females) to descriptively compare the intervention effects for consistency (same direction, similar magnitude). If the intervention effects are qualitatively different, we will formally test for an interaction between the moderator and the intervention variable in the mixed model. We acknowledge that we have limited power to detect meaningful moderating effects but we still plan to conduct the analysis to identify the subpopulations that may potentially benefit most from the intervention.

Treatment expectancy. We will directly evaluate participant's beliefs about the education program and compare them to participants in the mind-body program by collecting treatment

credibility and expectancy ratings. We do not anticipate any lasting therapeutic effects of the education program on the outcome measures. We do anticipate, however, that placebo and other non-specific effects that commonly result from participation in a group and in research studies will be seen in our participants,[130] and that comparison of the control group with the intervention group will help to determine the magnitude of these effects. We will compare baseline measures between non-responders and responders so that future mind-body interventions can be targeted to those most likely to benefit from them. We define responders as those participants who achieved at least a 2.5 point improvement on the RMDQ, and/or a 30% improvement on the MPQ-SF or 30% improvement on the NRS. We will look at each measure separately and jointly. Thus we will look at responders who have responded to one measure, as well as to those that responded to both function and pain measures.

Missing data, compliance, and dropout analyses. We do not expect substantial missing data due to the electronic nature of data collection which we have used previously. For instruments with several questions we will use the approach recommended by their authors for calculating total scores and composites when values for an item are missing. We will estimate compliance by the number of sessions attended and estimate the proportion of participants in each group with various levels of compliance. We also will calculate the proportion of participants missing each session to describe the pattern of compliance. Participants informing us they no longer want to continue in the study will be considered dropouts, and we will look at when these events occur separately in each treatment group. Dropout rates will be calculated as proportions of participants randomized, and as a cumulative probability of remaining in the study, using survival analysis techniques such as the product-limit estimator. Unlike proportions, the latter statistics, which can be estimated at various times following randomization, take into account when dropouts occur. As with the compliance measure, these statistics will be calculated separately for each treatment group. The information contained in these descriptive analyses may help us to devise strategies for keeping people in the study and attend all treatment sessions in future trials.

We anticipate 20% attrition at the assessment immediately following the 8-week program sessions based on our pilot work. Our sample size analyses have accounted for this amount of missing data. We cannot anticipate the attrition rate at 6 months and 12 months post study enrollment as we found it to be very low in our pilot work. We found older adults to be committed study participants. We would expect some deaths from natural causes during the course of the study because of the age of the study participants. Given this, we expect attrition to be low at 6- and 12-months. We will compare baseline characteristics between patients with the assessment immediately following the 8-week program to those without in order to assess potential biases that may exist in the complete case analysis. We will also try to obtain reasons for study drop out so that we can assess the missing data mechanism (missing completely at random, missing at random, non-ignorable missingness). At a single time point, we will conduct sensitivity analyses assigning poor scores and good scores for missing values differentially by treatment assignment to evaluate the impact on our study results.

We will use mixed models for our repeated measures analysis which are more robust to missing data than traditional multivariate models. Information at each time point influences estimates of treatment effects at other time points due to the specification of the covariance pattern. If the amount missing is large and appears to be different among treatment groups, we will conduct

sensitivity analyses with imputed data based on varying assumptions (ignorable vs. non-ignorable missing), data excluding persons with missing information, and data including persons with missing information.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Paperless Data Management System. We will employ a paperless data entry system which we have used in previous research studies that allows data to be directly entered into the data base. All information obtained-from screening to study measures-are obtained electronically. All measures are in electronic form and data entry customized to the study needs. The customized data entry system is then installed on the desktop computer or laptops used by study personnel. Access to data entry measures is password protected. Data are collected during one on one sessions with participants. This eliminates the need for and cost of double data entry for paper forms. It decreases missing and miss-entered data. It guides the data collector through these data collection tasks:

- Assigning a unique identifier to every participant
- Documenting Informed Consent
- Screening participants and determining eligibility
- Enrolling and randomizing eligible participants (to those allowed access to randomization)
- Collecting baseline and follow up data on enrolled participants

There is also a built-in tracking system that:

- Provides a "one stop shop" interface to organize participants and forms
- Ensures that only eligible participants are randomized and enrolled
- Displays a list of forms currently due for collection
- Displays completion status and date of all forms due

A relational database will be stored on a local network where only select research team members will have access to the database. The database will include routine data edit checks for consistency both within and between forms. Once edited, temporary files will be merged to generate files for data analysis. All files will be backed-up daily and archived weekly. Database development and maintenance will occur with Microsoft Access and the SQL Server available through the CRHC network. Analysis will be performed using SAS or Stata.

10.2 Data Management

The PI will oversee all aspects of data management. In the first three months of the study, an operations manual will be developed to standardize all procedures and staff training in areas such as participant recruitment, measurement, assessment, and data entry, management, and security. Data management will follow the policy and procedures of the Data Center (DC) (http://www.crhc.pitt.edu/DataCenter). All DC team members have been certified in their particular area of specialization.

10.3 Quality Assurance

This will be done by the following steps: 1) use of standard methods of data collection and

recording specified in a manual of operations, 2) a formal staff workshop on research integrity at the beginning of the study and when new personnel are hired, and 3) telephone audits on a random sample of participants to verify completion of interviews and data accuracy. Other data quality assurance measures will include detailed documentation of computer operations and data editing procedures and regular meetings with project staff to review any changes in procedure. The Data Center also has specific data quality measures that will be implemented. These include verifying the data, out of range data checks, and repeated evaluation of the data process.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB. A signed consent form will be obtained from the participant. The consent form will describe the purpose of the study, the procedures to be followed, and te risks and benefits of participantion. A copy of the consent from will be given to the participant and this fact will be documented in the participant's record.

11.2 Participant Confidentiality

All study participants will be assigned unique study identifiers that will appear on all data collection instruments, tapes, documents, and files used in the statistical analysis and manuscript preparation. Personal information needed for tracking and informed consent will be stored separately from other data with only limited team members having access to that data. No personal information concerning study participants will be released without their written consent.

11.3 Study Discontinuation

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

12. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by consensus among the investigators. Any presentation, abstract, or manuscript will be made available for review by the sponsor and the NIA prior to submission.

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