Title: Knee Arthroplasty Pain Coping Skills Training (KASTPain): A Randomized Trial

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Specific Aims

Recent data project that a total of 710,000 knee arthroplasty surgeries will have been conducted in 2010. By 2020, the frequency is predicted to more than double to over 1.5 million procedures. While arthroplasty is generally effective, approximately 25% of patients have unexplained disabling pain and impaired function a year or more after surgery, representing a significant cost to society in terms of lost productivity and medical costs.

Recently published evidence by our group and others indicates that pain catastrophizing predicts poor outcome and that pain catastrophizing is the most powerful psychological predictor of unexplained poor outcome. Pain catastrophizing identifies approximately 50% of patients who will have longer term disabling pain and impaired function (e.g., an estimated 89,000 patients in 2010). Pain catastrophizing is the tendency to magnify pain sensations, ruminate upon them, and feel helpless when experiencing pain. It is also amenable to treatment via pain coping skills training.

Pain coping interventions have been successfully implemented for patients with chronic musculoskeletal pain disorders, but have not been studied in a surgical population. Current practice guidelines for knee arthroplasty do not address the treatment of psychological distress, a major contributor to poor outcome. We propose to examine the efficacy of a pain coping skills training approach for patients scheduled for knee arthroplasty and who are at high risk for poor outcome. The proposed study will provide data that has strong potential to support a new treatment paradigm to improve upon current clinical practice.

Our long-term goal is to improve the outcomes for individuals receiving knee arthroplasty. In the current application, we propose a three-armed multicenter clinical trial; the "**Knee Arthroplasty Pain Coping Skills Training (KASTpain) Study**." The study extends work our team began with our R-34 funded grant. The **KASTpain** trial will test whether a pain coping skills training intervention improves the outcomes for arthroplasty patients with high pain catastrophizing pre-operatively, relative to arthritis education or usual care.

Specific Aim 1. To assess the efficacy of pain coping skills training in reducing knee pain and improving function. Our two primary hypotheses (to be tested in the clinical trial) are the following:

- **Hypothesis 1a.** Pain coping skills training is more effective than arthritis care education in *decreasing knee pain during functional activities*.
- **Hypothesis 1b.** Pain coping skills training is more effective than usual care in *decreasing knee pain during functional activities*.

We also will examine **one *secondary (hyp. 2) and one tertiary (hyp. 3) hypothesis***.

- **Hypothesis 2.** Pain coping skills training is more effective than arthritis education or usual care in improving self-reported function, physical performance, pain intensity, pain catastrophizing, and patient global ratings of improvement.
- **Hypothesis 3.** Pain coping skills training will reduce direct medical costs and indirect (i.e. patient time) costs relative to arthritis care education and usual care. When accounting for costs associated with pain coping skills training, the intervention will be cost saving or cost-effective relative to arthritis care education and usual care as measured by the incremental cost per quality-adjusted life-year.

Specific Aim 2. To determine if treatment benefits of pain coping skills are mediated by changes in pain catastrophizing:

- **Hypothesis 4.** Changes in pain catastrophizing that occur over the course of pain coping skills training will mediate treatment-related improvements in pain and self-reported function during recovery.

Research Strategy

Significance: Specific Aim 1

Knee arthroplasty surgery (TKA) is a common and generally effective procedure.[1] For example, projections estimate that 3.5 million procedures will be conducted annually by 2030.[2] Cost data for TKA also are impressive. Mean procedural charges per patient in 2003, reported in 2005 dollars, were $38,000 per primary surgery and $48,000 per revision surgery.[3] If these procedural charges data were extrapolated to the 2010 volume data projections, procedural charges would total approximately $28 billion dollars annually.

Serious early surgical complications such as venous thromboembolism or joint infection lead to poor outcome. However, the incidence of these adverse events is very low - on the order of 2% of all surgeries. Failure of the prosthesis is typically a late complication occurring several or more years following surgery and accounts for approximately 5% of poor outcomes.[4] The great majority of "poor" outcomes following knee arthroplasty are attributed to disabling pain and impaired function not attributable to early complications or prosthetic loosening. Pain is the predominant complaint of patients seeking total knee arthroplasty.[5-7] In large patient samples, improvements in pain or function scores have consistently been on the order of 40% to 60% relative to baseline, from 6 months to 2 years postoperatively.[8-16] However, some studies clearly elucidate the number of patients who respond poorly to the surgery. For example, Puolakka and colleagues found that 36% of 433 patients reported daily life disturbing pain and 27% had disturbed sleep four months or more after surgery.[17,18] Hawker et al. reported similar estimates 2 to 7 years following arthroplasty.[19]

Only a third of patients report no functional problems following surgery [20] and approximately 20% report dissatisfaction with their functional ability a year or more after surgery.[21] Functional deficits following surgery are observed in a wide range of activities, with up to 40% of patients still requiring the use of an assistive device to ambulate.[19]

The problem of disabling osteoarthritis (OA) pain and reduced function is a large and as yet unsolved problem that has a dramatic impact on quality of life and productivity. For example, revision surgery rates are impacted by persistent pain and impaired function. Roberts and colleagues conducted a survival analysis of 4400 patients with knee arthroplasty and found that 15 years following surgery, a total of 239 knees required revision and up to 35% were for unexplained pain. Extrapolating to current estimates, as many as 35% of 55,000 revision arthroplasty surgeries in the US in 2010 may be attributable to unexplained persistent pain and subsequent poor function.[22]

A barrier to progress in this field is that traditionally, knee arthroplasty has been presumed to be a highly effective procedure. The culture in clinical practice has historically been to forgo routine screening for patients at-risk for post-surgery persistent pain or compromised function. This culture has potential for change, however, because recent research has begun to acknowledge that unexplained poor outcomes occur. Predictors of these poor outcomes following knee arthroplasty are being identified. [23-26] Among the most consistent and powerful psychological predictors of poor outcome following knee arthroplasty is pain catastrophizing.[17,25,27-31]

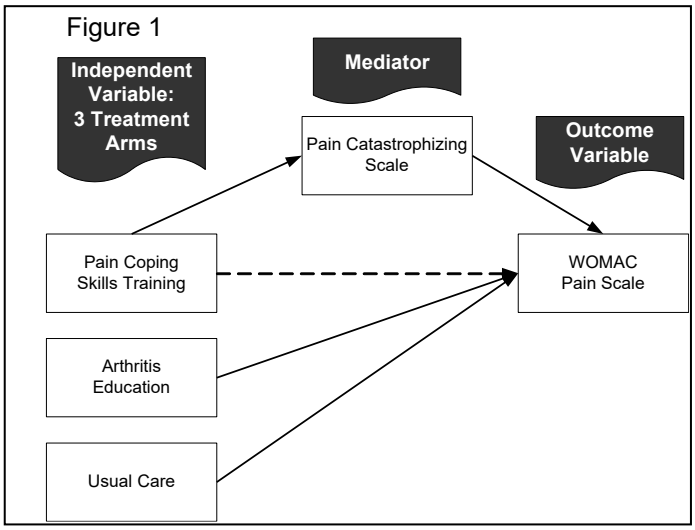
Additional impetus to address the issue of persistent pain was proposed by NIH. An NIH consensus panel was recently convened to review existing evidence on the use of knee arthroplasty surgery and to make recommendations for future research to improve the care for these patients.[32] The panel placed high priority on research examining the impact of perioperative interventions for these patients. Our proposed trial would specifically target this research need. If a high-quality trial demonstrated that pain coping skills training was successful at improving outcomes for at-risk patients with poor pain coping, and was cost effective, current clinical practice paradigms could be significantly improved.

Significance: Specific Aim 2

As Vlaeyen and Morley note, an important barrier to improving the effects of pain coping interventions is the use of a "one size fits all" approach to applying the intervention.[33] Systematic reviews have consistently demonstrated the efficacy of pain coping skills training and other forms of behavioral treatment for patients with a variety of musculoskeletal disorders.[34-36] However, effects generally are modest with effect sizes of 0.5 or less; a substantial proportion of patients receiving pain coping skills training do not appear to benefit.[37,38] Vlaeyen and Morley suggested that one way of improving outcomes is to better match the behavioral treatment to patient characteristics.[33] To address this issue, we have intentionally selected for treatment a sub-group of patients with high levels of pain catastrophizing, who we hypothesize will likely experience substantial benefits from pain coping skills training.

Testing for the presence of mediation (illustrated in Figure 1) will allow us to determine the extent to which pain catastrophizing[28,29,39] mediates the relationship between pain coping skills training and outcome. The dashed line between pain coping skills training and WOMAC Pain represents the hypothesized mediation (either partial or complete) of pain coping effects by pain catastrophizing. Understanding whether catastrophizing is a mediator for pain coping skills treatment response will provide a causative explanation for how pain coping skills training effectively improves outcomes following knee arthroplasty. If our study finds that pain coping skills training (CST) is effective and that pain catastrophizing explains these effects, the field of orthopaedic surgery could experience substantive changes in the way in which patients with knee arthroplasty are treated; to the benefit of many patients. Surgeons may begin to routinely screen for high pain catastrophizing and initiate pain coping skills training for selected patients.

Figure 1



Innovation: Specific Aim 1

Current clinical paradigms do not discuss formal identification of patients at-risk for poor outcome due to poor pain coping.[40] Nor do these paradigms address the use of perioperative interventions to reduce poor outcome risk. The current application challenges this practice paradigm. If our trial is successful, as we anticipate it will be based on our pilot work, the research will provide strong evidence to reconsider this traditional approach and may improve outcomes for thousands of patients who currently are at-risk for poor outcome.

Previous work by our group[29] and others[27,28,31,39] has identified a TKA patient subgroup at high risk for poor outcome. Patients with high levels of pain catastrophizing have been consistently shown to have a higher rate of persistent pain and compromised function compared to non-catastrophizers. Our study is innovative because it is the first trial, to our knowledge, to target a specific surgical subgroup of patients at risk for poor outcome. In addition, we completed a search of ClinicalTrials.gov and the World Health Organization registry portal on June 1, 2011 and found no trials examining the impact of pain coping skills behavioral interventions for patients with knee arthroplasty.

There is strong evidence from multiple systematic reviews that pain coping skills training and other similar behavioral interventions are effective for non-surgical patients with arthritis and other chronic conditions.[34,41,42] No studies were found that targeted patients undergoing surgery for chronic pain. Our proposed intervention is innovative in that it specifically focuses on cognitions and coping related to pain and was designed specifically for patients with knee arthroplasty. For example, the intervention accounts for the unique needs, interests and

concerns of patients who are undergoing knee arthroplasty surgery. Along these lines, the intervention addresses patient catastrophic thoughts and concerns about pain that can arise during recovery following knee arthroplasty,[14 43] and strategies for coping with pain and pain-related thoughts following knee arthroplasty. In summary, modifications we have made to CST make it uniquely well suited to address pain catastrophizing. The training format for each of the skills has been specifically modified to include training experiences that (1) help patients identify and evaluate maladaptive thoughts related to pain and (2) provide a means of teaching them to alter catastrophizing cognitions to more adaptive and realistic ones in order to reduce pain and improve function. While newer technologies such as web-based delivery show promise, current trial evidence is lacking for these technologies in an older OA patient group with high catastrophizing. Furthermore, our elderly sample would likely have difficulty with these new technologies. Research team members have successfully used similar interventions in numerous trials for patients treated medically for knee osteoarthritis, low back pain and spinal cord injury.[44-51] In sum, this body of work demonstrates the ability of the investigative team to organize and conduct innovative behavioral studies in patients with arthritis and chronic pain. While the intervention will be flexible to allow for individual patient preferences and differences, the essential elements will be well defined in both a therapist and patient manual that was developed during the R34 award. In addition, under the leadership and guidance from a nationally recognized expert in cost analysis (Dr. Shelby Reed) we will assess the cost effectiveness of the CST intervention. Our trial is innovative in that it will provide additional cost data for policy makers to judge the credibility of the intervention.

We have modified conventional coping skills training in ways that not only make it particularly well suited to address pain catastrophizing but that are also are quite innovative. Innovative features of the protocol include (1) a systematic approach to teaching patients how both the behavioral and cognitive pain coping skills they learn can be used to modify overly negative pain-related cognitions, and (2) a specific focus on helping patients who are prone to catastrophizing learn how to apply coping skills to the specific pain-related challenges associated with knee replacement surgery. Finally, studies of pain coping skills training routinely use self report outcome measures to assess effectiveness. Ours will be the first to include physical performance among our secondary measures to assess outcome, an innovative addition to outcome assessment.

Innovation: Specific Aim 2

Pain catastrophizing has been shown to mediate outcome of multidisciplinary medical treatment for chronic pain.[52-55] The KASTpain trial will be the first to determine if pain catastrophizing plays a mediating role in the context of a perioperative pain coping skills training intervention. By quantifying effects as illustrated in Figure 1, we will provide new insights into the temporal relationship of mediation effects of pain catastrophizing in patients receiving pain coping skills training immediately prior to, immediately after and several months following surgery.

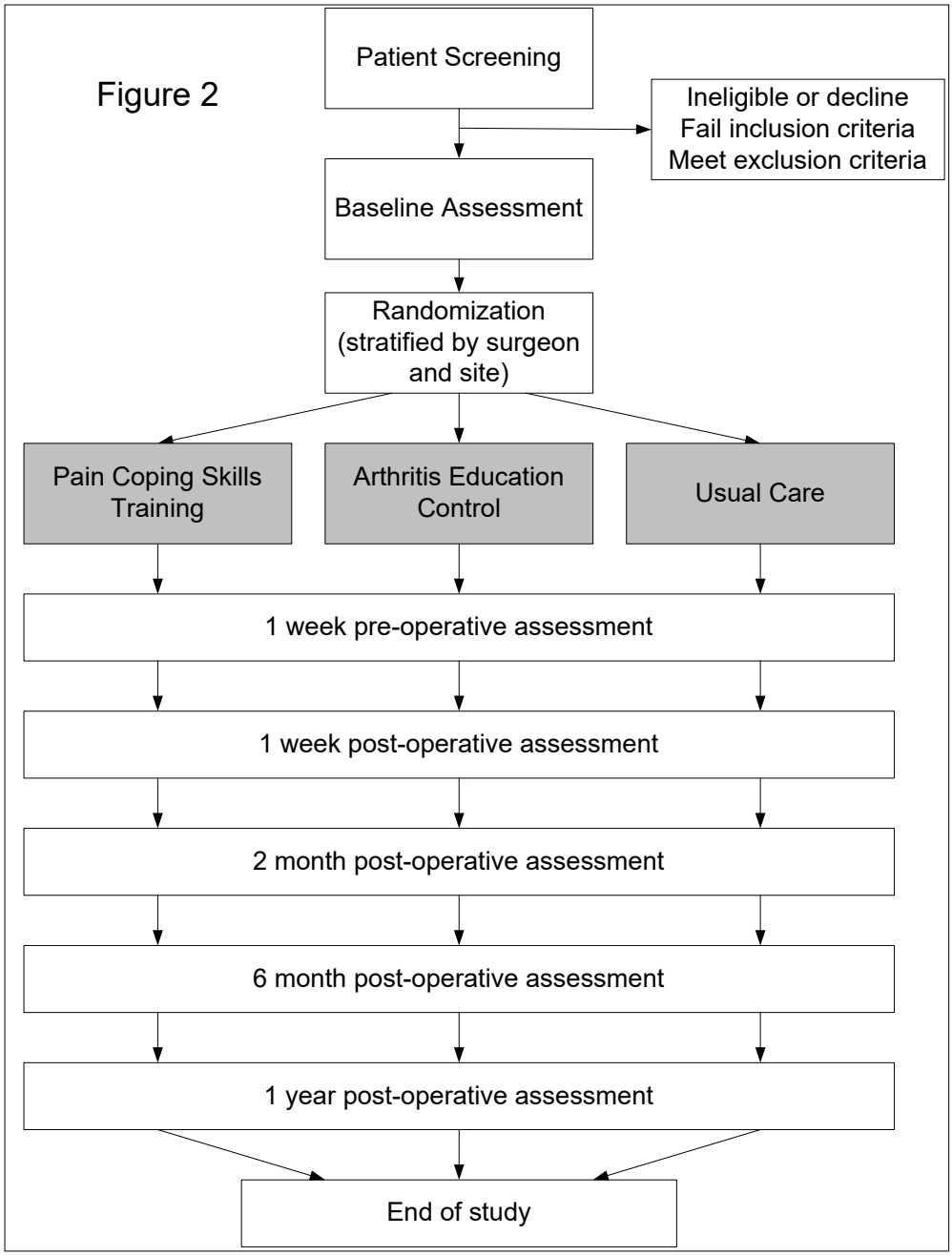
Approach: Specific Aim 1

Trial Design

The investigative team reached consensus on the final trial design during the R34 planning process. The KASTpain study will be a multi-center phase III randomized three-arm controlled trial designed to determine if pain coping skills training improves outcomes following primary knee arthroplasty to a greater extent than either an attention control arthritis education intervention or usual care.

Outcome assessors will be blinded to group assignment and patients randomly assigned to either the coping strategies training or arthritis education will be blinded to experimental group assignment to the extent that they will not be informed which group is believed to contain the key therapeutic elements (pain coping skills). Patients randomly assigned to usual care will not be blinded but assessors will be blinded to group

assignment. The eligibility criteria are designed to select a study sample with a Pain Catastrophizing Scale score of 16 or higher and therefore at high risk for poor outcome.[27-29,29,31] The primary outcome measure will be the WOMAC Pain scale, measured at 1 year following surgery. In addition, several secondary outcome measures also will be assessed (see **Primary and Secondary Endpoints** below). See Figure 2 below for a flow diagram of the planned trial.

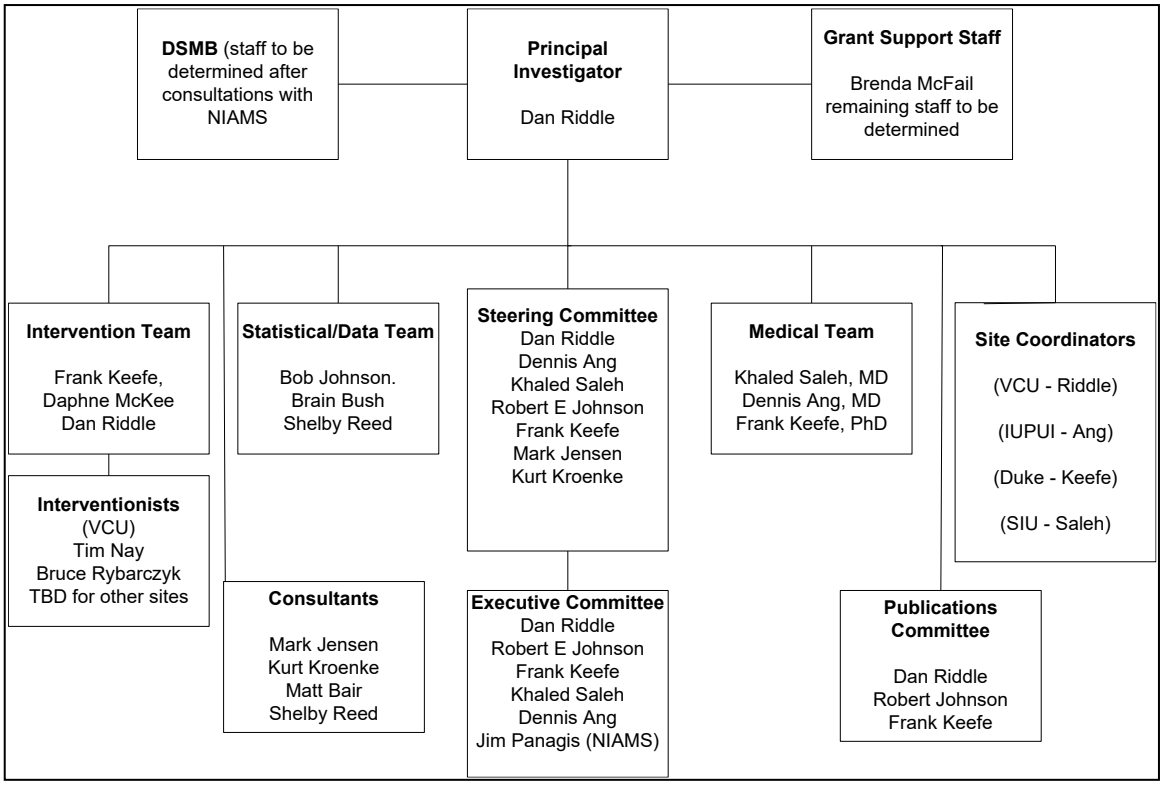


Description of the Study Organization and Administration

The organizational chart in Figure 3 below depicts the organization of the trial personnel. The coordinating center is Virginia Commonwealth University.

The PI will lead the trial and will chair conference calls and meetings of the Steering and Executive Committees (see below). The PI will also work in conjunction with the steering committee to assess study progress and to make modifications to the study plan when needed.

Figure 3



Steering Committee

The Steering Committee is responsible for the overall direction of a study. The specific duties of the Steering Committee will be to: (1) Prepare the essential study documents, including the protocol, protocol amendments, MOOP, and data collection forms; (2) review data collection practices and procedures; 3) modify study procedures as appropriate; (4) make appointments to or disband various study implementation committees as appropriate; (5) allocate resources based on priorities of competing study demands; (6) review study progress in achieving goals and take necessary steps to ensure the achievement those goals; (7) review and implement recommendations from the DSMB; and (8) review and respond to other general advice and/or recommendations (e.g., from the NIAMS Program Officer or other appointees). Table 1 below lists the members of the steering committee.

Table 1 Steering Committee for KASTpain Trial

Name	Academic Site
Daniel L. Riddle, PhD - Chair	VCU
Dennis Ang, M.D.	IUSM
Robert E. Johnson, PhD	VCU
Mark Jensen, PhD	UW
Frank Keefe, PhD	Duke Univ
Khaled Saleh, M.D.	UVA
Kurt Kroenke, M.D.	IUSM

Executive Committee

The Executive Committee is the smaller study leadership group that guides the study's day-to-day implementation and operation. This committee comprises the investigators coordinating research at each study site along with the biostatistician and the NIAMS program officer or representative. Table 2 lists the Executive Committee for the KASTpain study.

Table 2 Executive Committee for KASTpain Trial

Name	Academic Site
Daniel L. Riddle, PhD - Chair	VCU
Robert E. Johnson, PhD	VCU
Frank Keefe, PhD	Duke Univ
Dennis Ang, M.D.	IUSM
Khaled Saleh, M.D.	SIU
Jim Panagis or designated rep.	NIAMS

Publications Committee

This committee will plan the strategy for dissemination of the various publications resulting from the trial. The committee will be headed by Dr. Riddle. The committee will meet more frequently during the initial phases of the study to plan the publications and, in conjunction with input from other investigators involved with the study, begin planning a list of publications shortly after the study starts.

Statistical/Data Team

This group will work together to coordinate the data analysis and to address issues and concerns related to the data collection process. Dr. Johnson and Mr. Bush work closely together in the same department in the coordinating center (VCU) which should facilitate the rapid attention to any study related issues that impact data collection and storage. Dr. Reed, our health economist will work closely with Dr. Johnson during the data analysis phase of the study in conducting the cost analysis.

Intervention Team

This group has developed the treatment protocols to be used in the study. The team will work together to ensure that all interventions are applied and will conduct quality assessments of the interventions as defined in the MOOP. The Intervention team will be headed by Dr. Frank Keefe.

Medical Team

The medical team will address any medical concerns that arise during the study. This team will be involved with work by the DSMB in the unlikely event that modifications are needed to the study protocol. The team is made up of a Rheumatologist, a Surgeon and a Psychologist to address any potential medically related complication associated with the study. The team will be headed by Dr. Dennis Ang.

Coordinating Center

The roles and responsibilities of the Coordinating Center will be to: (1) train centers in all aspects of recruitment, retention and data capture; (2) develop and maintain the MOOP; (3) define the randomization scheme and ensure that all centers are properly trained to apply the scheme during the study; (4) assess the

validity and completeness of data flow and data tracking and address issues of Center adherence concerns to the steering committee; (5) develop procedures for data entry error identification and error correction; (6) train all centers in adverse event reporting; (7) communicate all aspects of study with participating centers; (8) make site visits to assure adherence to the study protocol and procedures; (9) institute and assess all quality control procedures, generate reports for the steering and executive committees and the DSMB; and 10) distribute all reports and updates of policies to all centers.

The PI will lead bi-weekly phone meetings with the site coordinators and PIs from each site as well as the monthly calls with the executive committee.

Clinical Sites

The roles and responsibilities of the Clinical Sites will be to: (1) Maintain the Site MOOP with revisions sent by the coordinating center; (2) Participate in site specific modifications to the study protocol related to patient recruitment to accommodate unique site characteristics; (3) assure that the study is conducted according to the protocol and the MOOP; (4) participate on the Steering Committee and other committees as appointed; (5) identify, recruit, screen, and enroll subjects, 6) protect the rights of all subjects; (7) obtain verbal consent during screening from each subject and obtain written informed consent as appropriate, from each subject; (8) demonstrate compliance and accountability with the study policy and procedures; (9) follow procedures regarding retention and forwarding of consent forms to data coordinating center; and (10) communicate any questions, concerns and key observations to the Principal Investigator and coordinating center.

Because all data collected during the study will be entered into a secure website, reports related to patient recruitment, data completeness, and timing will be generated by the Data Management Center. These reports will be provided to each site on a monthly basis.

Committee Meeting Schedules

Teleconference and in-person meetings will be held by the various committees based on the following schedule:

Steering Committee: Quarterly by phone.

Executive Committee: Monthly by phone.

Site Principal Investigators along with site study coordinators: Every two-weeks by phone.

Publications Committee: Twice a year meetings for first 2 years, then quarterly for remainder of study by phone.

Statistical/Data Team: Quarterly by phone.

Intervention Team: Quarterly by phone.

Medical Team: Quarterly by phone.

Investigator and consultant in-person meetings: This group will meet twice during the study. Because the team worked closely together during the R-34 funding period and after to develop the design and MOOP, there will be no meeting prior to the start of data collection. Rather, the first in-person meeting will be at approximately the midway point to assess study progress and make recommendations regarding any major revisions to assure completion of the study in the allotted time. The final meeting will be held at the end of data collection to review initial analyses and plan the writing of manuscripts on the final results and to plan other dissemination approaches.

Participants

Patients will be recruited from orthopaedic surgery practices in four centers: (1) Virginia Commonwealth University Medical Center; (2) Duke University Medical Center; (3) Indiana University; and (4) Southern Illinois University. Investigators from each site along with the PI have met with participating surgeons from the 4 centers and all have consented to participate (see support letters). Investigators at all sites have strong collaborative relationships with their orthopedic surgeon colleagues and, as part of our R34, have cemented these relationships over the last 2 years in preparation for the proposed trial.

The three major sources of treatment variation in knee arthroplasty are surgical technique, physical therapy and medication usage. A variety of surgical approaches and implants are available with no clear evidence of superiority among the options.[56] Surgeons are accustomed to conducting this surgery, for the most part, in the way that they were trained and to attempt to enforce standardization in surgical procedures was, in our view, unrealistic. In lieu of controls for surgical approach we will: (1) randomly stratify by surgeon and, (2) collect data from each surgeon on: (a) type of implant (i.e., cruciate retaining, posterior stabilized, rotating platform, patellar resurfacing (yes or no for each); (b) surgical approach (mid-vastus, sub vastus, medial parapetallar); and (c) use of cement (yes or no). These data will be collected for all patients and examined as potential covariates. Because surgical approach will not be standardized, there is no concern for a lack of equipoise among participating surgeons. Physical therapy for patients following TKR, in contrast, is generally similar across clinics in that the goal of physical therapy is to enhance functional status via range-of-motion and strengthening exercise and gait and balance training. There is no evidence of a clear benefit of any single physical therapy approach at one year. [57] To account for the duration (dosage) of physical therapy we will collect data on the total number of physical therapy visits for all patients and assess the impact of number of visits on outcome. Regarding medication use, we will track medication use in all three arms with a comprehensive medication list (see MOOP) to categorize the medication profile for each patient over the course of the study.

Chart abstractors blinded to treatment assignment will indicate if the patient had one or more of the following post-surgical complications: implant infection requiring surgery, implant failure requiring revision, implant loosening requiring revision, symptomatic DVT or PE, patellar dislocation or failure and knee fibrosis requiring manipulation. These complications typically require hospitalization or additional care and may influence outcome independent of the interventions being studied. Randomization will likely control for these effects, but we also will statistically adjust for the impact of these complications on study findings, if necessary. Overall, this pragmatic approach will, in our view enhance study generalizability.

Inclusion criteria will be the following:

- Adults 18 years of age or older and capable of providing informed consent.
- Diagnosis of osteoarthritis using American College of Rheumatology (ACR) criteria of moderate to severe knee OA[58] and function limiting pain as determined by the patients' orthopaedic surgeons.
- Scheduled for an elective unilateral total knee arthroplasty no sooner than 2 weeks or later than 8 weeks from the time of recruitment.
- Score of ≥ 16 on the Pain Catastrophizing Scale and ≥ 5 on the WOMAC Pain scale.
- Able to read and speak English.

Exclusion criteria will be the following:

- Scheduled for revision arthroplasty surgery.
- Unable to or declines consent for study participation.

- Self-reported diagnosis of inflammatory arthritis (i.e. rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosis, ankylosing spondylitis).
- Arthroplasty scheduled because of a fracture, malignancy or an infection.
- Scheduled for bilateral arthroplasty surgery.
- Scheduled for unicompartmental arthroplasty.
- Self reported plan to undergo hip or knee arthroplasty within one year after current knee arthroplasty.
- Presence of severe depression (20 or higher) using the PHQ-8 depression screener.[59,60]

Although it is possible that depressive symptoms could interfere with treatment efficacy, it is also possible that those with depressive symptoms might benefit more from the treatment than those who are not depressed, given that the intervention teaches skills that can help in the treatment of depression. By excluding only the participants with severe depressive symptoms, and including patients with other levels of depressive symptoms, generalizability will be enhanced and we will be able to determine if the intervention is more or less effective among persons with depressive symptoms, relative to non-depressed persons. In our pilot study of 112 knee arthroplasty patients with high pain catastrophizing as defined in our trial, a total of 3 patients (2.7%) had PHQ scores of 20 or higher. Depressive symptoms will be examined as a potential moderator of treatment effect in the analysis.

Other exclusion criteria were selected to reduce the risk of confounding in the trial. For example, patients receiving revision surgery have poorer outcomes as compared to patients undergoing primary knee arthroplasty.[56] Screening will be conducted via telephone by study staff after the patient has consented for surgery.

Randomization and Blinding

Participants who meet study inclusion criteria and consent to participate will be stratified by orthopaedic surgeon and randomized in permuted blocks of 3, one to each study group, to ensure that patients from each participating physician and site have an equal chance of being randomized to one of the 3 groups. Given that we will have 30 orthopaedic surgeons participating in the study (see Table 5 below), this approach will control for temporal and clustering effects resulting from single surgeons having imbalances in the numbers of patients in each treatment group over time. Assignment to one of the 3 groups will be accomplished with a computer generated table of random numbers created by the biostatistician and provided to the study coordinators at each site via a secure website. After collecting baseline data, each site's study coordinator will conduct treatment allocation by use of the study web site, allowing the treating surgeon and the follow-up data collectors (site coordinators and research assistants) to be blinded. We will instruct all surgeons of the importance of avoiding study contamination by not querying patients about study interventions. Surgeons also will be asked to report if they became aware of group assignment during the study. These data will be tracked and reported at the end of the study.

All data collected at each site will be obtained by data collectors who are blinded to group allocation. This will be accomplished by assigning patients to one of the three treatment groups using a secure website and then providing patients with treatment allocation information in random number matched pre-sealed opaque envelopes. Patients will be instructed to open envelopes once they return home and they will be asked not to mention their group assignment to the data collectors. Information in the envelopes will inform patients about group assignment and will instruct patients to contact site PIs if they have any questions about the treatment to which they have been assigned. Because site PIs will not be collecting data from patients, we will optimize the likelihood of keeping data collectors blinded to group allocation during the course of study.

Interventions

Pain Coping Skills Training

Patients assigned to pain coping skills training will have 8 sessions delivered by one of the sites clinical psychologists with experience treating patients with pain. There will be an initial in-person session approximately 1 month prior to surgery, six weekly telephone-based sessions with three prior to surgery and three during the 3 weeks following surgery, and one final in-person session approximately 1 month following surgery. Eight skills training sessions delivered over a 2 month period has been shown to be effective in several behavioral trials.[44-50] Use of telephone-based sessions is a new development in behavioral research and one which we have prior experience. It offers a cost-effective and practical approach for patients who have difficulty with mobility and travel.[61,62]

The pain coping skills training intervention was developed as part of our R34 funding and is based on information gathered in previous studies of chronic and arthritic pain by Keefe, Jensen and others,[45,54,55,63-68] as well as our pilot study.[69] The intervention is designed to modify coping strategies found to be related to pain and disability (please see the clinician training manual and the corresponding patient manual in the MOOP). The final protocol was based upon an extensive review of the literature, intensive discussions among the investigators, input from international experts working in the field of psychosocial interventions and pain catastrophizing, and our clinical experience working with OA patients who are high catastrophizers. There was consensus among all involved on three points: (1) that an overly narrow protocol, i.e. a simple attempt to use cognitive restructuring to alter catastrophizing only was unlikely to work because it would not examine the broader context in which catastrophizing cognitions occur for these patients; (2) that the CST protocol should not be as broad in scope or as intensive as comprehensive cognitive-behavioral therapy (CBT) interventions for pain; and (3) that CST should be used since it is the only intervention to date that has been shown in controlled studies to reduce both pain catastrophizing and pain.

The protocol to be tested is consistent with these three points. First, it includes training not only in cognitive restructuring but also a variety of skills that provide patients with opportunities to observe the impact of coping skills on changes in overly negative pain-related cognitions. Second, the CST protocol is neither as broad in scope nor is as intense as typical CBT interventions for general chronic pain. Rather, each of the skills included in our CST protocol was chosen *specifically because it provides a potentially potent means of helping patients identify and change their catastrophic pain-related thoughts.* We designed this CST protocol so that a key component of training for each of the skills is teaching patients how that they can use that skill to identify and reduce their catastrophizing. For example, patients will be trained in the coping skill “activity-rest cycling” and be taught how to monitor and change negative cognitions that arise as they apply this skill in daily pain-related situations. Application of this skill will help patients change from a cognition such as "I can't go for a walk around the neighborhood with my partner " to "I can go for walks if I break the walk up into periods of moderate activity followed by short rest breaks." Another example; patients will be trained in the coping skill of relaxation training and encouraged to identify and change negative cognitions as they apply this skill. For instance, prior to training in this skill a patient having a pain flare might think "I just can't relax when I am hurting" whereas after training they can learn to identify and then replace this thought with the thought "I have learned ways to relax and have used them during severe pain episodes in the past."

Protocol Description: Table 3 highlights the key elements of the CST protocol. The CST protocol will: (1) provide a rationale for the coping skills intervention; (2) train patients in cognitive restructuring as well as a variety of skills that provide patients with opportunities to observe the impact of coping skills on changes in overly negative pain-related cognitions; and (3) provide training in strategies for enhancing maintenance of gain following treatment. Rationale: To introduce the training, a simplified version of Melzack and Wall's gate control model of pain will be used to help patients understand that pain is a complex experience affected by

thoughts, feelings and behaviors.[70] Pain coping strategies will be described as skills that can be mastered through home practice. Training in coping skills: Cognitive-restructuring will be used to help the patient recognize the relationships between thoughts, feelings and behavior.[71] These techniques will teach them to identify irrational, maladaptive thoughts and to replace these with alternative, rational, reassuring and adaptive thoughts. A self-instructional training intervention developed by Turk and colleagues[72] will be used to help the patient use calming self-statements when dealing with severe pain. Activity-rest cycling and pleasant activity scheduling[73-75] will be used to reduce pain and enable patients to pace and increase their activity level. In activity-rest cycling, patients identify activities in which they overexert themselves (e.g., housework or shopping), learn to break those up into periods of activity and rest (e.g., 45 minutes of housework followed by 10 minutes of rest), and gradually increase their activity level as they decrease rest. Patients will identify activities they enjoy such as reading, doing crafts and hobbies, or visiting friends and then set and record weekly activity goals. Patients also will be trained in three attention diversion methods: relaxation, imagery, and distraction. Relaxation training, using a protocol and relaxation tape described by Surwit,[76] will involve concentrating on muscle tension signals and using them as cues to relax. Imagery will be taught as an adjunct to relaxation.[77] Patients will practice using pleasant imagery and changing from one image to another. Distraction techniques will include focusing on physical or auditory stimuli.[77] Maintenance Enhancement: Using relapse prevention methods, each patient will develop a written maintenance plan that includes the list of pain coping skills learned during the study, potential high risk situations, early warning signs of setbacks, and plans about how the patient might apply these skills in dealing with future setbacks and challenges.

Table 3 Key Elements of the CST Protocol

Training Objective	Coping Skill Training Methods
Altering Cognitions to Change Pain Catastrophizing	Cognitive Restructuring, Self-Instructional Training
Altering Activity Patterns To Change Pain Catastrophizing	Activity-Rest Cycling, Goal Setting
Using Attention Diversion to Change Pain Catastrophizing	Relaxation Training, Imagery, Distraction
Enhancing Maintenance	Relapse Prevention Training

Use of clinical psychologists to deliver the skills training may limit generalizability of our findings to settings with adequately trained psychologists. Because evidence is lacking on the use of lesser trained practitioners and because, in our experience, this patient population is particularly challenging given their higher levels of pain catastrophizing, we believe it is important to test the intervention using practitioners with advanced skills. However, we will plan implementation studies with non-psychologist practitioners if the results indicate that the intervention is effective.

Arthritis Education Comparison Condition

Patients randomly assigned to Arthritis Education, a comparison condition that will control for participation in a trial, time and therapist attention, will receive detailed educational information from a nurse educator about OA and its treatment. Nurse educators have similar levels of clinical experience as clinical psychologists, which will assist in making the argument that it is the content of the interventions and not the delivery of these interventions that we will be testing in the trial. The arthritis education sessions will use a presentation and discussion format similar to that originally described by Lorig for arthritis education.[78-80] The clinician and patient manuals were developed as part of our R34 funding (see MOOP). Figures and discussion sessions will present information on the nature of arthritis, what to expect following knee arthroplasty, treatment of osteoarthritis, the role of exercise, joint protection and making future treatment decisions.

This general approach to an arthritis education comparison condition has been used successfully in many behavioral studies and in several trials conducted by Keefe and Jensen.[44-50,55] Use of an education comparison condition enhances the scientific credibility of the study by testing whether the "pain coping" component of the experimental intervention effectively reduces pain and improves function over that seen in patients who receive a similar dose of time and attention from a health professional, but no specific pain coping skills.

Usual Care

Because the standard of care in joint arthroplasty includes no treatment directed toward poor pain coping, we have added a “usual care” group to determine real world effects of pain coping skills. Patients in the usual care group will only receive care that they would have routinely received had they not been entered in the study.

Economic Evaluation

Four types of information will be collected throughout the study for use in the economic evaluation: (1) all-cause medical resource use; (2) patient time; (3) health utilities; and (4) resources required to provide the coping skills training, arthritis education and usual care. We will collect information on all-cause medical resource use including hospitalizations, emergency department and urgent care visits, orthopedic-related procedures, medications for pain and/or inflammation, and outpatient visits, including sessions for physical and occupational therapy. This information will be ascertained via patient self-report and supplemented with medical records abstraction. To improve the accuracy of patient self-report, patient diaries will be designed to track medical resource use to record their estimates of time spent receiving the interventions, adhering to treatment recommendations (e.g. physical therapy), and employing coping skills.[81] Validity of patient diaries of medical service utilization is generally supported, particularly when instructions to patients are clear.[82,83] To incorporate potential differences in health-related quality of life experienced by patients in the three study arms into the cost-effectiveness analysis, we will measure health utilities using the 5-level EQ-5D (5L EQ-5D).[84] According to the EuroQoL group, preference weights for the 5L EQ-5D should be available by the end of 2012 (EuroQol Group Executive Office - personal communication). Finally, we will prospectively collect information on time spent by clinical psychologists and nurse educators and other individuals involved with the delivery of the study interventions as a basis for estimating intervention costs.

In accordance with recommendations for economic evaluation in health care, we will value costs from the societal perspective.[85] We will use standard cost assignment methods to estimate direct medical costs. To assign costs for inpatient care, we will assign Medicare diagnosis-related groups (DRG) codes and corresponding reimbursement rates, adjusted for differences in length of stay reported for patients in the study.[86,87] Medication costs will be based on the published average wholesale price (AWP) minus 16%.[88] Indirect costs associated with patient time will be valued using the average hourly wage in the US ($20.90, May 2009).[89] To estimate costs associated with the pain coping skills and arthritis education, we will apply a costing tool that we designed specifically to estimate costs associated with patient-centered interventions (5R01NR011873-02, manuscript in appendix 7). The tool applies scientifically-sound economic principles to assign costs to personnel, facilities, equipment, supplies, patient incentives and miscellaneous items.

Steps to Enhance Treatment Fidelity and Reduce Potential Biases

Because multiple sites will participate and increase the risk of bias due to differing approaches in applying the interventions, the research team will take a number of steps to ensure that the treatment protocols for coping skills training as well as arthritis education are delivered uniformly by all treatment providers involved in the study. First, all pain coping skills training will be implemented by clinical psychologists with experience treating patients with chronic pain. Second, all psychologists who participate in the study will receive coping skills training in workshops facilitated by Dr. Keefe and his team at Duke University. Experienced nurse educators will all be trained by Dr. Riddle to provide the arthritis education. Third, all psychologists and nurse educators

will be provided with detailed treatment manuals (as developed in the MOOP), and the treatment strategies will be taught through didactic instruction, taped illustrations of techniques from model cases, and role-play of common scenarios. Fourth, we will institute several "best practices" to enhance and monitor treatment fidelity of the pain coping skills training and arthritis education protocols which include: (1) careful attention to the treatment manuals; (2) intensive training onsite and at Duke University; (3) "real-life" enactment of treatment skills during training, and (4) on-line documentation of treatment delivery. Finally to provide supervision, all sessions for both groups will be audiotaped. These tapes will be reviewed in supervision sessions on a regular basis to ensure that the treatment manuals are being followed. Supervisors will provide feedback based on the review of these tapes. Remedial training will be provided to those clinicians who deviate from established protocol.

Treatment adherence, therapist competence and treatment credibility ratings will be collected from the two active intervention groups. Adherence refers to the extent to which a therapist uses interventions prescribed by a protocol. Therapist competence refers to the extent to which the protocol is delivered in a manner that is skilled and sensitive to patients' needs. Ratings of treatment adherence will be made by Drs. Keefe and Jensen (and by Dr. Riddle for the arthritis education arm) for a random selection of 10% of the sessions for each of the treatment conditions.[90] Protocol adherence rating sheets developed for each session will be used with satisfactory adherence defined as 90% or more of the maximum possible score on the adherence rating scale. Ratings of therapists' competence will be made using a 1 to 5 scale with satisfactory competence defines as an average of 4.0 or higher. Following the first treatment session, patients will complete a treatment credibility questionnaire developed by Devilly and Borkovec.[91]

With regard to study design, we will ensure the same treatment dose within and across treatment conditions (Pain Coping Skills Training vs Arthritis Education). We will monitor session attendance for coping skills training and arthritis education using a diary log with participant ID numbers and session dates to track percentage of attendance and to account for absenteeism and reasons for missed sessions. We will make every effort to deliver the full treatment, but we expect some variation in treatment delivery dose as well as treatment drop-out. Reasons for attrition will be assessed with an open-ended question for enrolled participants who withdraw. Drop-out reasons will be categorized and then judged by independent raters. Comparisons between the treatment conditions in drop-out rates will be made, and these rates will be included as covariates in the planned analyses if significant between-group differences emerge.

Loss to follow-up is always a threat in longitudinal studies. The following strategies will be employed to minimize loss to follow-up: (1) we will use up to 8 phone attempts to contact participants to schedule their post-treatment assessments; (2) we will obtain alternative phone contact information from each participant; (3) if we fail to contact a participant during follow-up phone contacts, despite multiple phone attempts, we will mail a reminder letter; (4) participants will receive up to $150 remuneration for study participation and this remuneration will distributed throughout the study period to be commensurate with study demands; and (5) we inflated our sample size by 20% to account for possible attrition.

Additional retention strategies will be employed in the study to reduce loss to follow-up as much as possible. For example, study coordinators will personally meet each patient enrolled in the study to develop rapport with each patient. The study website developed by the data coordinating center will provide study coordinators at each site with red-flag notices when patients miss their scheduled appointment dates by more than 48 hours. Study coordinators will be required to contact patients with missing data within 24 hours of receiving a red-flag notice. The PI will receive weekly reports from the data coordinating center so that the study investigators can discuss recruitment and retention during bi-weekly conference calls.

Preliminary Studies

Riddle has led and completed two published studies of the relationship between psychological distress and outcome following knee arthroplasty. The first was a secondary analysis of a cohort study of 952 patients and was published in 2007.[92] Our findings suggested that surrogate measures of general psychological distress (like the mental health score of the SF-36) did not provide adequate fidelity and that more precise measures of specific psychological states and disorders were necessary.

To test this hypothesis a second study was undertaken to determine if more specific measures of psychological distress (i.e., depression, anxiety, self-efficacy, fear of movement, pain catastrophizing) predict pain and functional outcomes following knee arthroplasty.[29] After adjusting for confounding factors, pain catastrophizing was the only consistently strong psychological predictor of poor WOMAC Pain outcome (Odds ratio = 2.7, 95%CI=1.2, 6.1). We found that 60% of patients with high pain catastrophizing had a poor outcome, (defined as a WOMAC Pain change score of <50% from baseline to 6 months post surgery) as compared to 30% of patients with low catastrophizing who had poor outcome. Other studies have reported similarly strong findings indicating that pain catastrophizing predicts pain and function outcome following knee arthroplasty.[27,28,30,31]

Pilot Intervention Study

The research team recently completed a quasi-experimental study of the efficacy of the proposed pain coping skills intervention.[69] We recruited 18 knee arthroplasty patients from two sites (Duke University and Virginia Commonwealth University) to participate. All patients met the inclusion criteria as defined in our proposed trial and received the pain coping skills training intervention. WOMAC Pain and Disability scores and PCS scores were collected prior to surgery and 2 months following surgery. Data from patients receiving pain coping skills training were compared to a historical cohort of 45 patients who also received knee arthroplasty and had high pain catastrophizing (≥ 16 on PCS), but received no pain coping skills training. ANCOVA adjusting for baseline scores was used to compare the patients in the treatment group to the historical cohort. The Group (coping skills training vs usual care) X Time (pre-op vs follow-up) interaction was used to estimate the magnitude and significance of the treatment effect.

Patients in the pain coping skills group demonstrated a mean improvement in WOMAC Pain scores of 6.9 (sd = 4.7) points while patients in the historical cohort achieved a mean improvement of 2.6 (sd = 4.8) points. Differences among groups were highly significant with effect sizes ranging from .71 to .96. for WOMAC Disability, WOMAC Pain and Pain Catastrophizing.

Respondent burden was assessed by asking participants to complete a 16-item questionnaire (2 items for each coping skill) that assessed the extent to which each skill was helpful and how frequently the skills were used. Patients rated each skill as being somewhat to extremely helpful and patients indicated they used each skill at least weekly to more than once per day. These data suggest that patients found the skills to be therapeutic and useful during their recovery.

In summary, our preliminary work and the work of others[27,28,31,39] strongly suggest that: (1) pain catastrophizing is a key psychological variable that adversely impacts pain and functional outcomes in patients following knee arthroplasty; (2) our proposed intervention has strong potential for producing clinically important improvements in self-reported pain and functional status in patients who are at high risk for poor outcome; and (3) the feasibility of the intervention is high and can be delivered efficiently in multiple sites.

Pilot Physical Performance Battery Study

We undertook a second pilot study to determine the feasibility of using a well defined physical performance battery for patients following knee arthroplasty. Associations between self-report and performance measures are moderate, on the order of r = .5, suggesting they measure different patient attributes.[93-97]

Because there is no agreed upon standard set of performance-based measures for patients with knee arthroplasty, we chose to pilot a six-minute walk test a measure that is reliable and captures changes in distance walked and pain perceived throughout the recovery period.[93,94,98]. The Short Physical Performance Battery (SPPB) combines two simple balance tests a 4-meter walk test and a repeated chair stand test into one summated score. The SPPB has been studied extensively and found to be significantly reduced in persons with knee arthritis as compared to healthy age-matched persons[99] and is responsive to changes following interventions designed to improve mobility.[100,101]

We recruited a consecutive series of 10 patients 1 year following knee arthroplasty to determine if the SPPB and the six minute walk test would be well tolerated. In addition, we were concerned about possible ceiling effects on the SPPB which can occur with high functioning elderly persons.[102] SPPB total scores range from 0 to 12. The mean score on the SPPB summary scale for the patients was 8.5 (sd = 2.3) and ranged from 3 to 11. We concluded that the SPPB and the 6-minute walk test are well tolerated by patients receiving knee arthroplasty and that some individual tests comprising the SPPB will likely demonstrate ceiling effects. We will therefore use the composite SPPB score and a time-based calculation of the composite SPPB score[103] in addition to the 6-minute walk test.

Primary and Secondary Outcome Measures and Endpoints

Participants from all three arms will be evaluated by an assessor who is blinded to group allocation at baseline, 1 week prior, and 1 week after, 2 months, 6 months and 1 year after surgery. The baseline assessment will include age, gender, comorbidity[14,104], education and occupation, current medications, mental healthcare received and a variety of pain and psychological characteristics including depression, anxiety, pain coping etc. Follow-up outcomes will include measures of pain, function, catastrophizing and depression. (see MOOP in appendix for a complete description).

The primary outcome measure and endpoint will be the WOMAC Pain scale measured 1 year following knee arthroplasty.[105-109] The WOMAC has been studied extensively and its scales have been shown to be reliable and valid for quantifying the extent of both pain and disability in patients undergoing knee arthroplasty.[16,110,111] Secondary outcome measures will be the WOMAC Disability scale, Pain Catastrophizing Scale (PCS),[112-114] a verbal pain rating scale,[115,116] and a patient global rating of change scale measured on a numerical rating scale from -5 (vastly worse) to +5 (completely recovered) and measured 2 months, 6 months and 1 year post-surgery.[117-119] The timeframes were chosen because the trajectory of recovery following knee arthroplasty is non-linear and we want to track changes associated with the intervention during the course of the study.[10,13,94] Two performance-based measures, the 6-minute walk test [93,98] and the Short Physical Performance Battery will be assessed at baseline and 1 year post-surgery.[120] Routine follow-up visits are typically scheduled with the surgeon at 12 months following surgery. Planning follow-up measures to coincide with routine patient visits to their surgeon or other provider will be a cost-effective and clinically feasible way of collecting follow-up data with minimal burden. All sites will have the space necessary to conduct the performance-based tests. This is the first study of a pain coping skills training intervention that has used performance-based measures to assess efficacy. This battery of primary and secondary outcomes addresses the key domains of outcomes recommended by IMMPACT, a consensus based group of experts in the area of pain treatment outcomes.[121,122]

Sample Size Estimations

The primary endpoint will be the WOMAC Pain score at 1 year. Changes of 2 or more points in the 20 point WOMAC Pain scale indicate clinically important differences between individual patients.[123-126] We powered our study to detect a difference of at least 2 points between the pain coping skills group and the arthritis education group. Our pilot study showed a larger difference of 4.2 points (with an effect size of .74) between the coping skills group and the usual care group two months following surgery. We will use a more conservative treatment

effect of 2 WOMAC Pain points for coping skills training for three reasons. First, our pilot study used a quasi-experimental design which may overestimate treatment effects because of non-randomization. Second, estimates were based on comparisons to usual care, and we suspect that some therapeutic benefit will be experienced by the arthritis education group. Third, these data represent only short-term changes following surgery and most patients continue to improve up to a year following surgery.[9,14]

Using a two-sided two group 0.05-level t-test of differences in means and assuming the intervention difference minus the arthritis education control difference is at least 2.0 WOMAC Pain points, a sample size of 107 in each group will have 91% power to detect this difference, assuming that the common standard deviation is 4.34 (based on pilot work described earlier). This corresponds to an effect size of 0.46 which is consistent with the effect of other behavioral interventions for knee arthritis.[127-129] This sample size also adequately powers the study to detect a 20% difference between groups in the number of patients with a 50% or greater improvements in WOMAC pain relative to baseline scores. [9,10,12-15,130] This effect will be equivalent to an odds ratio of 2.25 and is equivalent to a Numbers Needed to Treat (NNT) of 5 which is indicative of an effective intervention.[131] The revised CONSORT statement endorses use of indexes such as number needed to treat.[132]

Thus, the total required sample size is 321 (107 patients per arm) for the planned 3-arm trial. Based on our pilot study, we expect 5% attrition due to early drop-out resulting from cancelled surgery. Patients who undergo surgery and drop out due to lack of interest, unrelated medical illness or loss of follow-up also will be included in the intent to treat analysis. Our pilot study of 18 patients suggests this number will be on the order of 10%, although this estimate is likely to be low because the pilot study was only 2 months in duration. Our previous work with similar types of patients suggests that loss to follow-up will likely be closer to 20% one year following surgery.[14,29] Therefore, 402 patients (134 patients per study arm) will need to be enrolled in the trial (321+64 due to loss of follow-up+17 due to cancelled surgery). A total of 2,100 patients will need to be screened because our pilot studies indicated that approximately 19% of the screened sample will actually participate (ie. they will meet all inclusion and exclusion criteria AND provide consent for the study). Stratification by surgeon and by site is expected to reduce outcome variability and thereby increase power.

Data Analysis

Intention to treat (ITT) will be the primary approach for all analyses and, depending on the pattern of missing data (missing at random, completely at random or not missing at random), multiple imputation using SAS StAT/MI methods will be used to impute values for those lost to follow-up.[133] In addition, we will compare the ITT analysis to the results for patients who actually undergo surgery to determine if undergoing surgery affects the findings. For the primary analysis, the effect of treatment will be assessed using linear mixed models with time as a repeated factor. The model will account for correlation over time within participants, correlations within clinics, surgeons, and baseline covariates. Surgical approach, complications, medication and physical therapy use will be assessed for potential effects.

Estimates of the effect of pain coping skills training will be obtained by constructing linear contrasts to compare the mean change in outcome from baseline to each of the key time points (2 months, 6 months and 1 year) between the pain coping skills group and the two control groups, with adjustment for the other variables. Analyses of the secondary outcome variables will be conducted using a similar approach. For the analyses using dichotomous outcomes of ≥50% improvement at 6 months and 12 months, generalized linear models with logistic regression will be used to compare the proportion of patients with ≥50% improvement after adjustment for baseline data.

Our study is powered to detect clinically important differences in WOMAC Pain scores among treatment groups. As an additional secondary analysis, we also will examine the effects of potential moderators. Moderators are baseline characteristics that predict treatment effects.[134] Additional psychosocial issues may influence treatment effects in knee arthroplasty patients with high levels of pain catastrophizing. Potential

moderators for patients with knee arthroplasty who may particularly benefit from pain coping skills training are the following: expectations prior to surgery[135-137], self efficacy[138,139], extent of social support[9,140] and depression.[27] Recent evidence suggests that psychological states of depression, low expectations for recovery from surgery, poor self-efficacy and reduced social support increase risk of poor outcome following surgery, and may therefore modify the effects of pain coping skills training. Because our study is not powered to test for these potential moderators, they will be assessed only for the primary outcome of WOMAC Pain at 1 year. This analysis will be performed by including a three-way Moderator X Treatment group X Time interaction term in the mixed models analyses. It is our intent to assess whether these variables independently predict those patients who are more likely to respond to pain coping skills training versus arthritis education or usual care. Pain coping skills training emphasizes pain coping strategies, unlike usual care or arthritis education and because of this emphasis, we suspected that coping strategies training would be particularly effective in patients with less healthy psychosocial features. Knowing whether any of these potential moderators actually predict response to treatment will aid in better identifying individuals who are more likely to respond to the intervention.

Cost Analysis

We will conduct a cost analysis to compare mean total costs incurred over the one year follow-up period in the KASTpain study between patients randomized to coping skills training vs. arthritis care (and vs. usual care). We will compare each component (medical costs and indirect costs) and estimate intervention costs. All three components will comprise total costs which will also be compared. Total costs, from the societal perspective, will consist of direct medical costs, intervention-related costs and indirect costs. From the health care system (or payer) perspective, indirect costs will be excluded. Sensitivity analyses will be performed to evaluate the impact of scaling up the intervention (i.e. more patients per session; fixed costs allocated over more patients) and methodological choices for cost assignment.[141,142]

Cost-Effectiveness Analysis

The incremental cost effectiveness ratio (ICER) will be calculated as the difference in the mean cost per patient between study arms divided by the difference in estimated quality-adjusted life-years (QALYS). Mean costs will be estimated as described above. Quality-adjusted life-years will be estimated using utility estimates derived from the EQ-5D. Because the interventions represent fixed-, one-time costs while the benefits of the interventions may last beyond the one year follow-up period in the KASTpain study, we will conduct sensitivity analyses that extrapolate differences in utilities measured at the end of follow-up over 3, 5, and 10 years, assuming that the interventions do not differentially impact survival. If we observe statistically significant differences in costs (not including intervention costs) between treatment arms at 12 months, we will extrapolate treatment-specific cost estimates over 3, 5, and 10 years, consistent with the time period for QALYs. We will evaluate uncertainty by estimating 95% CIs for estimates of costs, QALYs and measures of cost-effectiveness (i.e. ICERs or net health benefits[143]) using nonparametric bootstrapping.[141,142]

Timetable and Milestone Plan

The milestone plan is as follows:

Enrollment of the first subject*:* Prior to enrolling the first subject, all sites will be required to complete IRB approval procedures and interview, hire and train research staff including the clinical psychologists and nurse educators. All study staff will be required to complete training in the study protocol as described in the MOOP and will also require time to develop working relationships with orthopaedic surgery staff in preparation for patient recruitment and retention. Clinical psychologist training will require travel to Duke University while the PI will travel to each site to train the nurse educators. We expect to have all IRB, hiring and training procedures

completed and should be fully prepared to begin study recruitment within 6 months of the beginning of the study. Assuming that the study will begin on April 1, 2012, the first subject will be recruited by October 1, 2012.

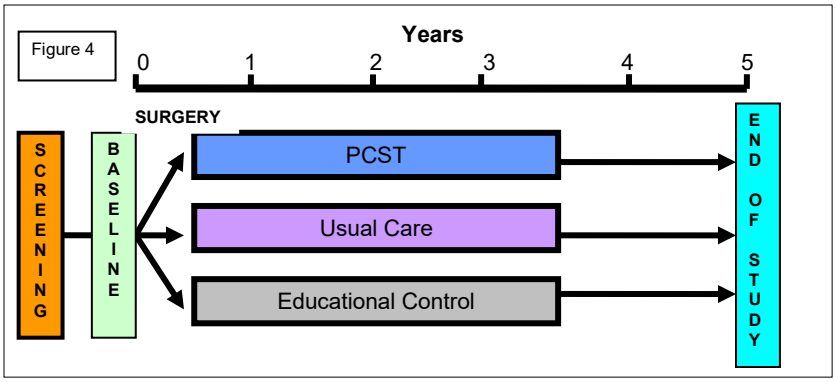
25%, 50%, 75% and 100% enrollment projections: We expect enrollment for these various thresholds to occur by the following time periods listed on Table 4 below. The recruitment period will require, at maximum, a total of 3 years.

Table 4 Summary of Recruitment Goals

Recruitment Goal (% of target sample recruited)	Estimated Date of Completion
25%	July 1, 2013
50%	April 1, 2014
75%	Jan 1, 2015
100%	Oct 1, 2015

Completion of data collection time period: We will complete data collection one year following recruitment of the final subject which will be October 1 of 2016.

The flow of the study over the course of the 5-year study period is summarized in figure 4 below.



Completion of primary and secondary data analyses: We estimate that analyses of primary and secondary endpoints will be completed by February of 2017.

Completion of final study report: We plan to complete the final study report at the end of the grant funding period during the month of April of 2017.

We expect subject enrollment to require 36 months. This estimate assumes that a total of 100 or 101 subjects will be enrolled at each site (n=4 sites). Our sample size estimations based on our pilot studies (see Sample Size Estimation Section above) indicated that we would need to screen a total of 2100 patients to successfully recruit the requisite number of 402 patients. Table 5 below indicates that approximately 1,768 patients undergo primary knee arthroplasty for OA at the four sites each year for a total of 5,305 patients in a 3 year period. We would need to screen approximately 40% of the total sample of patients from each site to meet our recruitment goals and we believe this to be realistic and feasible. Every attempt will be made to recruit the requisite number of patients from each site, so that each site is equally represented in the analysis. However, if one or more sites have difficulty meeting recruitment goals, the large number of total patients in the four sites should allow us the flexibility to recruit additional patients from sites that are seeing more patients. Because we have been working with the sites for two years as part of our R34 development, we do not expect sites to drop out or to have problems with recruitment. However, we have recruited two additional sites (see letters attached) to participate should we need to recruit additional patients. The duration of the clinical trial is estimated to be 5 years (See Figure 4).

Table 5 Estimated Sample Size at Participating Sites

Clinic site	# of Surgeons	Primary TKAs during 3 year recruitment period	Estimated number eligible and consenting	Total needed for study
VCU	3	865	164	100
SIU	12	2210	420	101
IU	7	780	148	100
Duke	8	1450	276	101
Totals	**30**	**5305**	**1008**	**402**

Data Coordinating Center

All data collection services will be coordinated through our Department of Biostatistics Data Management Group (DMG), housed in the Department of Biostatistics at Virginia Commonwealth University. This center provides state-of-the-art data collection, management, reporting, and analysis services to Virginia Commonwealth University's clinical and translational researchers. DMG will provide secure data services for all aspects of data gathering including web based data form development for data collection, reminders and completion reports for data collectors at each site and for the executive committee, electronic data acquisition, server storage repository, randomization procedures for each site, study staff entry of performance data and tracking of visit data (including no-shows and dropouts) for clinicians providing the interventions. The Biostatistician will work closely with the Director of the DMG to assure a seamless, sound and secure process of data collection, storage and analysis.

The web and database servers will reside on centralized Virginia Commonwealth University servers behind the University's firewall. Web-accessible systems will be protected by appropriate security measures, and utilize Secure Sockets Layer (SSL) encryption for transport security. Data storage will be centralized, with regular off-site backups performed by trained IT personnel. Only the investigators and other approved personnel will have access to study data, at a level commensurate with their responsibilities. Appropriate consideration will be given to subject's identifiable information.

In addition to the above safeguards, VCU employs a network Intrusion Prevention System (IPS) that analyzes data packets on the networks for known signatures of probes, intrusion attempts, IP spoofing and other suspicious activities. System event logs from network devices and host applications are reported to Cisco Security Monitoring, Analysis, and Response System (MARS) to improve threat identification, mitigation responses, and compliance.

Periodic and ad-hoc reporting will be utilized to show subject recruitment and retention data stratified by site. Automated email agents will electronically notify site staff and investigators of upcoming and overdue subject follow-ups. Upon request, the data manger will provide de-identified data in a form agreeable to the biostatistician. In addition, the DMG will provide timely troubleshooting assistance via phone and email and answer inquiries from research staff and investigators. The investigators will develop a User's Guide to aid the study staff with data management tasks should the study be funded.

Approach: Specific Aim 2

We will collect Pain Catastrophizing Scale, WOMAC Pain and Disability Scale and a verbal pain rating scale scores on all patients at six time points (4 to 6 weeks prior to surgery, 1 week prior to surgery, 1 week following surgery, 2 and 6 months following surgery and 1 year following surgery). Our rationale is that we want to capture the short- and intermediate-term temporal progression of changes in catastrophizing prior to and following treatment to describe changes in mediation over time. The primary outcome measure will be the WOMAC Pain scale, collected at all assessment points. The independent variable will be treatment condition (Pain Coping Skills Training vs Arthritis Education vs usual care). (Figure 1)

Our hypothesis is that the effects on WOMAC Pain by the pain coping skills arm will be either partially or fully mediated by pain catastrophizing, whereas effects by arthritis education or usual care will either not be mediated by pain catastrophizing or mediated to a significantly lesser extent as compared to the pain coping skills arm. Mediation will be investigated using the three-step approach described by Baron and Kenny[17] and modified for randomized trials by Smeets and colleagues.[144] A series of 3 multilevel regression analyses will be used to determine if pain catastrophizing mediates the effect of the interventions on pain as measured with the WOMAC Pain scale at the various time points. WOMAC Disability and verbal pain rating scores will serve as secondary outcome measures for the mediation analysis.