Preventing Persistent Post-Surgical Pain and Dysfunction in At-Risk Veterans: Effect of a Brief Behavioral Intervention

Short Title: Preoperative Pain and Rehabilitation Education (PrePARE)

Principal Investigators:

Barbara Rakel, RN, PhD, FAAN
Associate Professor, University of Iowa College of Nursing

Lilian Dindo, PhD
Assistant Professor, Baylor College of Medicine

Supported by:
National Institute of Nursing Research

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clinicaltrials.gov: NCT03965897

University of Iowa IRB-03 VA: 201811822
University of Iowa IRB-01: 201812794
Baylor University IRB: 42053 VA ID: 19B03.H

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Protocol

University of Iowa
Baylor College of Medicine

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Table of Contents

PRÉCIS

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Objectives

Using a multi-site, double-blind, two-arm, parallel, randomized controlled trial with Veterans at-risk for PPSP post-TKA, the following aims will be addressed:

1. Primary Aim: To examine the superior efficacy of ACT versus Attention Control (AC) on postoperative pain intensity and functioning in at-risk Veterans undergoing TKA. Changes in pain intensity and functioning from baseline to 6 weeks, 3 months and 6 months post-TKA will be compared. Level of pain intensity will be measured using the BPI Pain Severity Subscale and level of functioning will be measured using the KOOS Activities of Daily Living and Quality Of Life Subscales.

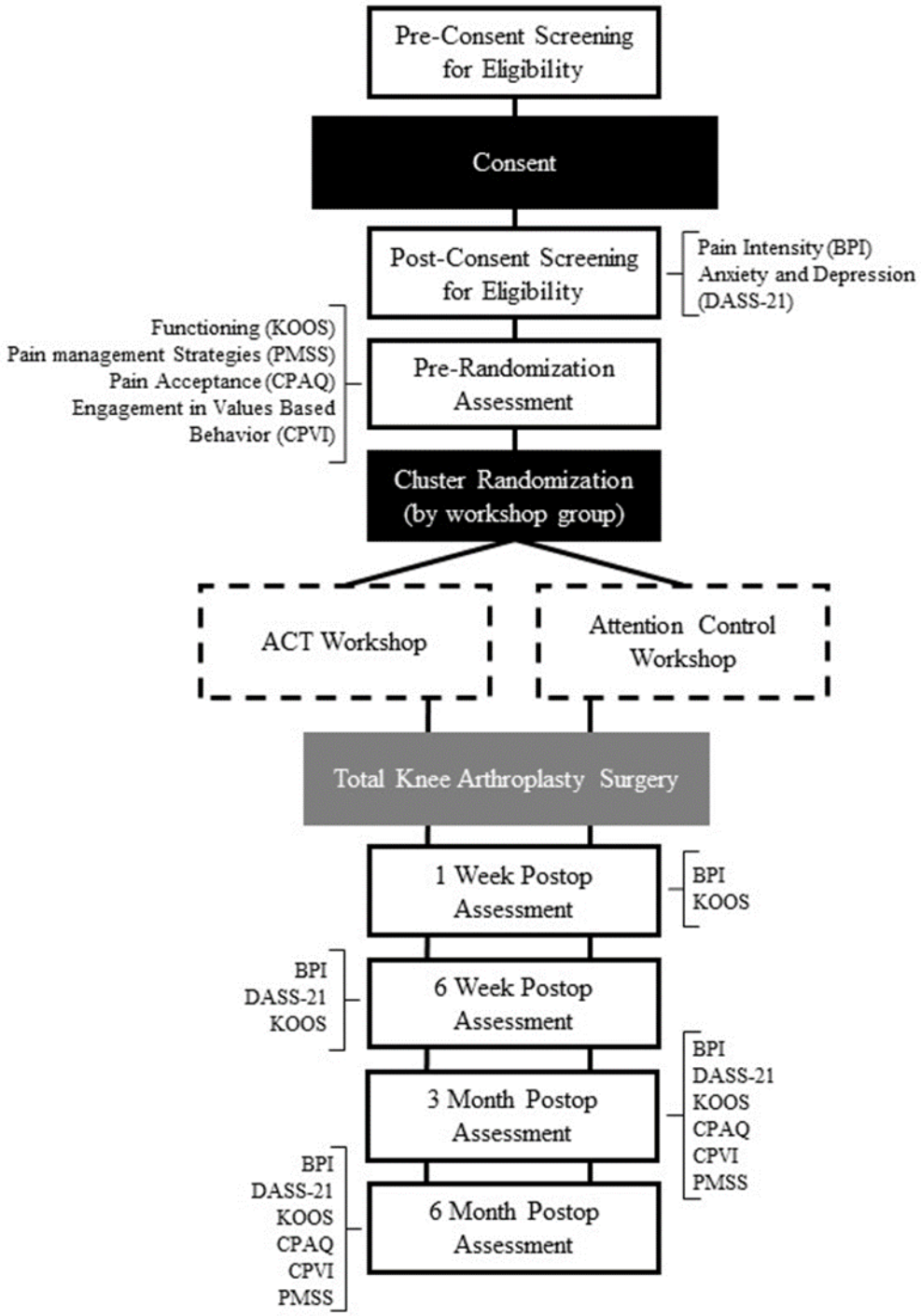
2. Secondary Aims: A) To examine the superior efficacy of ACT versus AC on the severity of anxiety and depressive symptoms and improvements in coping skills. Changes from baseline to 6 weeks, 3 months and 6 months post-TKA will be compared. Anxiety and depressive symptoms will be measured with the Depression, Anxiety and Stress Scale (DASS-21). Coping skills (i.e. Pain Acceptance and Engagement in Values-Based Behavior) will be measured with the Chronic Pain Acceptance Questionnaire and the Chronic Pain Values Inventory. B) To evaluate whether decreases in distress-based symptoms and increases in coping skills mediate changes in pain and functioning at 6 months in Veterans receiving ACT. Changes in anxiety symptoms, depressive symptoms, pain acceptance and engagement in values-based behavior from baseline to 6 weeks and 3 months will be used as potential mediators for changes in pain and functioning at 6 months.

3. Exploratory Aim: Describe the pharmacological and non-pharmacological strategies Veterans are using to manage pain and their perceived helpfulness. This will provide insights into the effects of the current opioid restrictions on pain management strategies. These strategies & their perceived helpfulness will be assessed using the Pain Management Strategies Survey at baseline, 6 weeks, 3, and 6 months.

Study Design

The proposed study is a multi-site, double-blind, two-arm, parallel, randomized controlled trial. At-risk Veterans will be randomly assigned to one of two groups: 1) Acceptance and Commitment Therapy (ACT); or 2) Attention Control (AC). Primary and secondary outcomes will be measured at 6 weeks, 3 and 6 months but 6 months will be the primary outcome endpoint for determining mediator effects. Data collected at postoperative week 1 will be used as potential moderators of treatment response.

Schema


Pre-Consent Screening for Eligibility
Consent
Post-Consent Screening for Eligibility
Pain Intensity (BPI)
Anxiety and Depression (DASS-21)
Functioning (KOOS)
Pain management Strategies (PMSS)
Pain Acceptance (CPAQ)
Engagement in Values Based Behavior (CPVI)
Pre-Randomization Assessment
Cluster Randomization (by workshop group)
ACT Workshop
Attention Control Workshop
Total Knee Arthroplasty Surgery
1 Week Postop Assessment
BPI
KOOS
BPI
DASS-21
KOOS
6 Week Postop Assessment
3 Month Postop Assessment
BPI
DASS-21
KOOS
CPAQ
CPVI
PMSS
BPI
DASS-21
KOOS
CPAQ
CPVI
PMSS
6 Month Postop Assessment

Inclusion and Exclusion Criteria

The target study population is veterans undergoing unilateral total knee arthroplasty (TKA) who are at-risk for persistent postsurgical pain (i.e. report moderate to severe preoperative pain in the presence of anxiety and/or depression OR report severe pain and absent anxious and depressive symptoms). A total of 430 participants (215 per group) will be recruited to achieve 150 subjects per group.

Inclusion Criteria

Participants must meet all the following inclusion criteria to participate in this study:

- Veteran;
- 18 years old or older;
- Having unilateral total knee arthroplasty (TKA);
- At risk for pain, anxiety, depression and/or stress, or pain catastrophizing defined as 1, 2, 3 or 4 (below):
    1. Worst pain greater than or equal to 7 on BPI (severe pain)
    2. Worst pain 3-6 (moderate to severe pain) on BPI AND anxiety symptoms (anxiety score greater than or equal to 6 on the DASS 21 or DASS stress score greater than or equal to 10)
    3. Worst pain 3-6 (moderate to severe pain) on BPI AND depressive symptoms (depression score greater than or equal to 7 on the DASS 21)
    4. Worst pain 3-6 (moderate to severe pain) on BPI AND PCS score greater than or equal to 20

Exclusion Criteria

All candidates meeting any of the exclusion criteria will be excluded from study participation. Exclusion criteria are:

- Inability to complete study forms because of language/literacy barrier;
- Bipolar or psychotic disorder;
- History of brain injury (moderate to severe TBI, other severe injury);
- Cognitive impairment (documented in medical record and/or MIS-T score of less than 4);
- ACT therapy within the past year;
- Inability to attend workshop prior to surgery;
- Imminent risk of suicide (including recent, related hospitalization);
- Indicated surgery is revision of TKA

Termination

Participants will be terminated from the study if they do not have surgery within approximately one year of attending workshop

Re-approaching Potential Participants

Consented participants who do NOT meet inclusion criteria before their surgery may be rescreened, re-approached, re-consented and reassessed for eligibility if they are indicated to have a second TKA surgery before the end of the study enrollment period. These participants will be eligible for this reassessment no earlier than eight weeks after their first TKA.

Data Analysis

Descriptive statistics (means, medians, percentages, standard deviations, and inter-quartile ranges) of all variables will be computed for each intervention group. We will describe sex and race/ethnicity results separately to identify potential differences, based on these biological variables. The distributions of continuous variables will be evaluated for normality. If data are non-normal, statistical analyses appropriate for non-normal data will be utilized (see below). Variables will be compared across intervention groups using a t-test for continuous variables, Wilcoxon-rank sum test for ordinal and non-normally distributed continuous variables, and Pearson Chi-square test for categorical variables. Variables that are found to significantly differ between the groups will be used as covariates in the comparison of outcome measures between the treatment groups.

Intent-to-treat (ITT) analyses will be conducted to assess treatment efficacy on post-operative outcomes using all subjects that have been randomized and had surgery performed. Only those who receive surgery are included in these analyses to test the efficacy of ACT on the primary and secondary outcome measures because our underlying model for treatment effectiveness is based on the assumption that ACT will prevent the development of PPSP by helping Veterans cope with postoperative pain. Therefore, receipt of surgery is inherent in our treatment model. Follow-up data on randomized subjects that did not have surgery will be included in a secondary analyses that will contrast the effect of ACT between those with and without surgery.
For variables in the primary aim (pain severity and functioning), efficacy of ACT compared to AC at 6 weeks, 3 months and 6 months will be tested using linear mixed model analysis for repeated measures. The fixed effect in the model will include intervention group, time, and intervention*time interaction effect. The model will also include site, workshop (cluster) within intervention, and subject as random effects. Test of mean contrast will be used to compare between treatment group means and mean change from baseline to 6 weeks, 3 and 6-months post-TKA between ACT and AC. P-values will be adjusted using Bonferroni's method to account for the number of tests performed. The efficacy of ACT versus AC will be expressed as the group mean difference with a 95% confidence interval (CI), using the SAS STAT (14.1) MIXED procedure.

For the secondary aim (A), efficacy of ACT compared to AC on anxiety symptoms, depressive symptoms, pain acceptance, and engagement in values-based behavior will be compared using linear mixed model for repeated measures. Intervention group mean differences will be estimated and tested as described in the analysis for the Aim1 variables.
For the primary and secondary aim analyses, it is expected that randomization will lessen the need for covariate or moderator adjusted analyses. However, if any demographic, baseline, time from workshop to surgery, or perioperative variables (i.e. perioperative anesthesia/analgesic, postoperative complications, postop day 1 pain and function, etc.) are found to differ between intervention groups, the model will be expanded to include these variables as covariates or effect moderators to estimate and test intervention group mean differences, or odds ratio, controlling for these variables.

In addition to the analyses described above for the primary & secondary outcome measures, similar linear mixed model analyses that include all randomized subjects will be performed. This secondary analysis will include surgery status in the model to contrast the impact of the intervention on those with and without surgery.

For the secondary aim (B), mediation analysis will explore the causal pathway between intervention (ACT or AC) and change in pain intensity and functioning from baseline to 6 months with decreases in anxiety and depressive symptoms, and increases in acceptance-based coping and engagement in values-based behaviors from baseline to 6 weeks, and baseline to 3 months as mediators. With the independent variable X (intervention) randomized to workshops (clusters), and the mediator variables M (decreases in anxiety and depressive symptoms and increases in acceptance-based coping and engagement in values-based behaviors), and the dependent variable Y (changes in pain & function) measured at the subject level within clusters, we have a two-level hierarchy with a 2-1-1 design. For this multilevel design, multilevel structural equation modeling (MSEM) will be used to estimate and test the direct and indirect effects to assess multilevel mediation as described by Preacher, Zyphur, and Zhang105 using SEM in Stata.

In the case of subject drop-out, reasons for subject drop-out will be recorded and compared between treatment groups. Subject characteristics and outcome measures collected prior to drop-out for those that drop out post-surgery will be compared to those that complete the study. In the presence of missing data, under the assumption of missing at random (MAR), linear mixed model analysis which can handle incompletely observed subjects and uses a likelihood estimation method will provide correct likelihoods and lead to valid estimates.106 Similarly, the use of the weighted GEE method is able to handle missing responses caused by dropouts in a longitudinal study.107 However, since the data under analysis cannot distinguish if data is MAR or it is missing not at random (MNAR), sensitivity analysis will also be performed using pattern mixture models. Multiple imputation will be used for sensitivity analysis by imputing from a non-random pattern mixture model.108

For the exploratory aim, frequencies for each pharmacologic and non-pharmacologic pain management strategy will be calculated to describe the types of strategies reported at each visit. Patterns (from baseline to 6 months) and trends (i.e. changes over the 4 year data collection period) will be examined. Helpfulness ratings will be averaged using means and standard deviations or medians and interquartile ranges for each strategy to provide insights on strategies at-risk Veterans find helpful. Differences in types and helpfulness of pain management strategies by treatment group will be explored.

Sample Size

Sample size was estimated using KOOS-Activities of Daily Living Subscale (the primary outcome requiring the largest sample size). According to the literature, a change of 8 points or more represents a clinically significant improvement.85 Therefore, assuming an average of 6 participants per workshop (cluster), with an ICC of 0.06 and a standard deviation of 18, a sample size of 300 Veterans (n=150 per treatment group) will be needed to detect a clinically

significant difference of 8 at a 0.0167 significance level (adjusted for testing at 3 time points) with 0.80 power. Assuming 20% will have surgery cancelled/postponed due to health issues and 10% will drop out after randomization (17% and 10%, respectively, was observed in our R34 study), we plan to enroll 430 Veterans to ensure that we will have n=150 per treatment group for the primary aim analyses. Veterans who do not have surgery after randomization will be followed over a similar timeframe and will be included in the secondary analyses.

Recruitment, Consent and Enrollment

Summary of recruitment and consent process, in-person

Identifying Patients

In order to increase awareness of the study, flyers describing the study will be posted in the orthopedics clinic and copies will be made available for patients to take. The study's Research Assistant (RA) will use Vista to identify all patients scheduled in the VAMC Orthopedics Clinic for a knee pain consultation. The RA will then review these patients' medical records to determine if they speak English with adequate competence AND do not have a diagnosis of dementia, bipolar or psychotic disorder, or history of brain injury. They will also review prior orthopedic notes to gauge readiness for surgery.

Approaching Patients

If during the consult the provider determines the patient should be considered for TKA, the RA will approach the patient in clinic to describe the study and ask if they would like to participate. They will be provided with a verbal description of the study objectives and procedures and given the opportunity to ask questions.

Screening for Exclusion Criteria

If the potential subject is interested in participating, the RA will identify any exclusion criteria through the administration of the pre-consent screening survey and by administering the MIS-T. If any exclusion criterion is met or if the participant scores less than 4 on the MIS-T, the RA will terminate the recruitment effort.

Consenting

If the patient is willing to participate, all sections of the informed consent document and the HIPAA authorization form will be reviewed with the patient, including sections on risks and benefits and voluntary nature of the study. A consent summary and a visual diagram of participation will also be shared with the participant. Adequate time will be provided for the patient to read the consent form themselves. The RA will be prepared to answer any questions. In order to minimize any possibility of feelings of coercion to participate, potential participants will be told that their decision (to participate in the study or not) will not affect the clinical care he/she receives. If the patient is still interested, they will be asked to sign one copy of the form and will be given another copy to keep for their records. They will also be asked to complete the PrePARE Subject Compensation Form in order for study personnel to arrange payment for participation.

Summary of recruitment and consent process, over-the-phone

Approaching Patients

If the RA is unable to approach the patient in clinic or if the patient would prefer to take information home and think about it, a flyer and a letter will be given or sent to the patient to provide basic, introductory information about the study. Approximately one week after delivering/sending the letter, the RA will telephone the potential subject to describe the study objectives and procedures and answer any questions. The letter will contain instructions to notify the study team if they do not wish to participate or be contacted, otherwise the RA will call until they are able to contact the potential participant.

Screening for Exclusion Criteria

If the potential subject is interested in participating, the RA will identify any exclusion criteria through the administration over-the-phone of the pre-consent screening survey and by administering the MIS-T. If any exclusion criterion is met or if the participant scores less than 4 on the MIS-T, the RA will terminate the recruitment effort.

Consenting and Post-Consent Screening for Eligibility, In-Person Appointment

If the patient is eligible and remains interested, the RA will schedule an in-person appointment to review the consent form (and HIPAA) and complete the screening process. A letter reminding the participant of this appointment will be sent. During this in-person appointment, patients will again be provided with a verbal description of the study objectives and procedures and given the opportunity to ask questions. If the patient is willing to participate, all sections of the informed consent document will be reviewed with the patient, including sections on risks and benefits and voluntary nature of the study. A consent summary and a visual diagram of participation will also be shared with the participant. Adequate time will be provided for the patient to read the consent form themselves. The Recruiter will be prepared to answer any questions. In order to minimize any possibility of feelings of coercion to participate, potential participants will be told that their decision (to participate in the study or not) will not affect the clinical care he/she receives. If the patient is still interested, they will be asked to sign one copy of the form and will be given another copy to keep for their records. They will also be asked to complete the PrePARE Subject Compensation Form in order for study personnel to arrange payment for participation.

Consenting and Post-Consent Screening for Eligibility, Over-the-Phone Appointment

If the eligible patient is unable to meet in person to go through the consent process, but is still interested in participating, the RA will offer to obtain informed consent (and HIPAA) and continue the screening process over the phone. If the eligible patient is agreeable to this approach, a letter, two copies of all consent documents, the contact information sheet and compensation form will be mailed to the patient. The RA will contact the patient approximately one week after sending the materials to review the consent document and the HIPAA authorization form with the patient and answer any questions they may have. In order to minimize any possibility of feelings of coercion to participate, potential participants will be told that their decision (to participate in the study or not) will not affect the clinical care he/she receives. If the subject is still interested, confirms they have reviewed the consent document and agrees to sign and return the consent documents, the participant will be asked to complete the contact information form. They will also be instructed to return a signed copy of the consent, HIPPA authorization form, and completed contact information form using a pre-addressed and stamped envelope. Consents received in the mail will be examined for accuracy. If a participant has not signed, initialed and/or dated their consent correctly, it will be returned to them with a letter ("Consent Corrections letter.rtf") containing instruction for correcting it. If a participant fails to return their consent, a new consent will be sent along with a letter reminding them they must sign and return the consent form before compensation can be processed.

Consented participants who do NOT meet inclusion criteria before their Total Knee Replacement (TKA) surgery, may be rescreened, re-approached, re-consented and reassessed for eligibility if they are indicated to have a second TKA surgery before the end of the study enrollment period. These participants will be eligible for this reassessment no earlier than eight weeks after their first TKA.

Consented participants who do NOT meet inclusion criteria before their scheduled Total Knee Replacement (TKA) surgery may be rescreened, re-approached, re-consented and reassessed for eligibility if their surgery is cancelled and there is a significant delay to it being rescheduled (due to COVID-19 surgery restrictions, for example).

Summary of post-consent screening and pre-randomization assessment

Consented participants will be asked to complete the Agreement to Participate; Demographics, SCQ, BPI, PCS and DASS 21. This should take 20-30 minutes. Participants who meet inclusion criteria (Worst pain greater than or equal to 7 on BPI [severe pain]; OR worst pain 3-6 [moderate to severe pain [on BPI AND anxiety symptoms [anxiety score greater than or equal to 6 on the DASS 21 or DASS stress score greater than or equal to 10]; OR worst pain 3-6 [moderate to severe pain] on BPI AND depressive symptoms [depression score greater than or equal to 7 on the DASS 21]; OR worst pain 3-6 [moderate to severe pain] on BPI AND PCS score greater than or equal to 20) will then be instructed to complete a set of surveys (i.e., OQ-45.2; CAGE; DAST-10; PCL-5; KOOS - baseline; STAI-Trait; PMSS (baseline); CPAQ; CPVI; PROMIS sleep: COVID impact). Completing these surveys should take approximately one hour. These surveys may be completed online on paper. The medical record will be reviewed for this same information (i.e. demographics, medical information, medications). Any discrepancies in medical information will be discussed with the participant to facilitate complete and accurate data. Once completed, participants will be scheduled for a workshop and asked to order their lunch (if attending an in-person workshop). Participants will also be given instructions for accessing the post-op surveys online through REDCap and given contact information for study personnel.

Participants who have completed the pre-randomization assessment will be considered "enrolled".

Study Interventions

Veterans will attend either a 1-day ACT workshop or a 1-day AC workshop prior to surgery. These workshops may be held online via Zoom to minimize risk of exposure to COVID-19. Two psychotherapists, trained in ACT, will provide the workshops in groups of 3-10 Veterans. Each workshop will last 5-6 hours.

Participants will be allowed to take breaks and lunch will be provided (at in-person workshops only). Participants will be sent an invitation approximately 2 weeks before their scheduled workshop, a reminder letter 1 week before the workshop and, if they have consented to participate in the Department of Veterans Affairs' Annie mobile Short Message Service (SMS) text messaging, a short text message reminding them of the workshop. They will also receive a reminder call and message one day before the workshop. If participating in an online Zoom workshop, the participant will be sent instructions for using Zoom and a link to join the workshop via their own computer/tablet or they will be sent an iPad via registered mail with the link bookmarked. A research team member will also call the participant the day before to review the instructions for connecting to the virtual workshop. If a participant fails to attend their scheduled workshop, they will be contacted to reschedule. If they repeatedly fail to attend a workshop and do not respond to attempts to reschedule, a letter will be sent requesting they contact the study.

ACT

The ACT workshop will cover the following topics 1) Acceptance and Mindfulness Training emphasizing new ways of managing troubling thoughts, feelings, and physical sensations (e.g., learning how to recognize, and develop cognitive distance from, unhelpful thoughts such as “I can’t take this pain anymore” or “This is unfair”) and learning how to willingly face experiences that cannot be changed; and 2) Behavioral Change Training involving a) teaching patients how to recognize ineffective patterns of behavior and habits, b) exploring and setting life goals and goals related to mental and physical health, and c) promoting effective and committed actions to achieve these goals despite the urge to do otherwise. Participants in the ACT workshop will receive two manuals and a deck of therapy cards. At the end of the ACT workshops, ACT participants will be asked to document a goal that will be reviewed at the booster session.

AC

The AC workshop will cover the following topics: a) the pathophysiology of postoperative pain and how it differs from preoperative pain, b) the role of contextual factors (e.g., depressive or anxiety symptoms, expectation) on the experience of pain, d) the role of inflammation in pain and healing, e) types of pain medications and other pain relief strategies provided following surgery, and f) goals of pain medications. Participants in the AC workshop will receive one manual.

Booster

A research team member will consult with each participant at their workshop to schedule the "booster" session and all postop assessments. They will also, again, be given instructions for accessing the post-op surveys online through REDCap. Two weeks after surgery, one of the workshop facilitators will call participants to check on them and conduct an individualized phone “booster” session. This phone call will

last 20-40 minutes. A second booster, lasting 20-40 minutes, will be conducted if any of the following occurs: 1) the participant reports within the 6-week assessment window that there are surgical complications, new health problems, and/or emotional issues that are affecting recovery and/or causing significant distress, 2) a study psychologist determines within the 6-week assessment window that there are surgical complications, new health problems, and/or emotional issues that are affecting recovery and/or causing significant distress, 3) the participant has surgery four or more months after attending a workshop. Participants will receive a reminder call/message approximately 1 day before the session. Participants who have consented to participate in the Department of Veterans Affairs' Annie mobile Short Message Service (SMS) text messaging, will receive a short text message reminding them of their scheduled "booster" session a day before the session.

Randomization

This study will use a cluster randomization approach where the unit of randomization will be the workshops. Randomization will occur right before each workshop so that all participants attending that workshop will be randomized to that intervention (i.e. ACT vs. AC). Statistician Dr. Zimmerman will generate the randomization sequence to ensure adequate distribution of the two interventions over the study period. Randomization will be stratified by site (i.e. Iowa City versus Houston). The randomization sequence will be maintained by the Statistician in a password protected file. This file will be used to generate concealed envelopes maintained and accessed by a facilitator at each site. Allocation of workshop to intervention group will remain concealed for facilitators until approximately one week before the workshop to allow for the needed preparation. Workshop allocation to intervention group will remain concealed for all other study personnel and participants until the beginning of the workshop when all invited participants have arrived. Those in attendance will receive the assigned intervention. This allocation approach will eliminate pre-treatment withdrawals, minimize the potential for experimenter and participant bias by protecting the randomization sequence in a central location, maintain concealment of treatment allocation until the last possible moment, and keep the participants and outcome assessors blinded to treatment.

<u>Virtual Workshops</u>
The randomization scheme for BCM should be used for all virtual workshops.

Blinding

This is a double-blind study. Participants are blinded to which treatment is the treatment of interest and outcome assessors will be blinded to which treatment participants receive. The treatment allocators (i.e. project coordinators) and the workshop facilitators will not be blinded so they can be available throughout the study to answer questions regarding treatment. It is essential for them to know which group the participant is in, in case they need to troubleshoot the treatment.

Participants will complete the Workshop Usefulness Survey (Workshop Question 6wk) in REDCap at the end of their 6-week assessments and the Participant Blinding Question in REDCap at the end of their 6-month assessment. Assessors will complete the Assessor Blinding Question (Workshop Question 6mo) in REDCap at the end of each participants' 6-month assessment.

Post-Op Evaluations

6 Weeks, 3 Months and 6 Months Post-Op Surveys

At 6 weeks, 3 months and 6 months postop, all Veterans will receive REDCap automated survey invitations and, if they have consented to participate in the Department of Veterans Affairs' Annie mobile Short Message Service (SMS) text messaging, short text messages reminding them to take the survey. If participants prefer, paper copies of these surveys will be mailed to them with a cover letter. At 6 weeks, the survey will include: BPI; DASS-21; PCS; OQ-45.2; KOOS - postop; CPAQ; CPVI; Promise Sleep; Complications; and workshop usefulness (6wk). At 3 months, the survey will include: BPI; DASS-21; PCS; PMSS (postop); OQ-45.2; KOOS - postop; CPAQ; CPVI; and Promise Sleep. At 6 months, the survey will include: BPI; DASS-21; PCS; PMSS (postop); OQ-45.2; KOO - postop; CPAQ; CPVI; Promise Sleep; Workshop Usefulness (6mo); and COVID-19 Impact.

Survey Review

In each case, after the participant has completed the surveys, the RAs will cross-check the medications reported in the BPI and DASS-21 with those in the medical record and discuss discrepancies with the participant.

Data Collection and Quality Assurance

Data management

The Study Coordinator at the Coordinating Site will be responsible for:

1. Designing and maintaining the REDCap data collection site as well as the Tracking Database
2. Ensure all data is stored so that blinded study personnel do not have access to any data that would un-blind them.
3. Conduct regularly scheduled audits (including hard-copy-to-electronic-copy checks) and data quality checks

REDCap

All data collection forms will be available through a REDCap (Research Electronic Data Capture) database (supported by the institutional CTSA) and patients can directly enter data into these forms. They will enter data into a central database through their computer or a tablet provided in the clinic. This will eliminate error in data entry, and reduce time necessary for data entry, cleaning and analysis. Range checks will be programmed into the data entry system when the nature of the data allows so that it will not permit invalid values to be entered into the database.

When a data collection session is completed, the RA will review electronic forms for completeness and validity. The RA will resolve all queries and will enter an override for all values that have been confirmed as being accurate. Reports will also be run periodically to confirm or correct questionable values. All changes will be tracked through the REDCap audit trail.

The data entered into the REDCap database is stored on servers at the University of Iowa and is backed-up on a regular basis.

Data Locations

Locations of confidential participant records

1. Tracking Database: Password protected electronic database stored on the VA server, accessible only to IRB-approved study personnel.
2. REDCap: Password protected online data capture software. Data is encrypted and stored on a secure UI server, accessible only to IRB-approved study personnel.
3. Locked filing cabinet for all personnel: A locked filing cabinet devoted to the purpose of securing participant charts and consent forms accessible only to IRB- approved study personnel.

Locations of data by type

1. Participant details (ID, medical record ID, current status [active, declined, withdrew, lost, etc.], current stage in study [chart screened, phone screened, pre-randomization complete, etc.], etc. are recorded in the Tracking Database.
2. Chart Review: Charts reviewed by research assistants. Patient ID, name and contact information recorded in Tracking Database on the secured VA server. Findings recorded in REDCap and essential findings ("passed initial screening" or reasons for not passing this initial screening) also recorded in Tracking Database.
3. Pre-Consent Screen: Pre-consent screen completed by research assistants. All findings recorded in REDCap and essential findings ("passed screening" or reason/s for not passing screening) recorded in Tracking Database.
4. Consent and post-consent screening: consent procedure and screening findings recorded in REDCap. Completed consent form to be printed and filed in individual subject files. IRB approval date of signed consent form is also recorded in Tracking Database. Consent forms to be filed together alphabetically in locked filing cabinet.
5. Pre-randomization assessments: All data collected and stored in REDCap; date completed also recorded in Tracking Database
6. Treatment allocation recorded in REDCap instrument accessible only by unblinded personnel.
7. Booster sessions: All data collected and stored in REDCap. Date completed also recorded in Tracking Database
8. Postop Assessments: All data collected and stored in REDCap. Date completed also recorded in Tracking Database
9. Log of protocol deviations maintained in the Tracking Database; paper report forms to be filed together by ID in locked filing cabinet
10. Recordings of workshops and fidelity ratings: (S:) IOW Services Drive\Research Rakel Closed\PrePARE

Strategies for minimizing missing data

Strategies will include:

1. Reviewing all surveys for completeness before finalizing
2. Conducting weekly texts and/or phone calls, as needed, to remind participants to complete daily logs
3. Contacting participants postoperatively to review data entry requirements, provide them with verbal and written directions for filling out and submitting daily logs, reviewing contact information, and identifying appropriate methods/times for follow-up contacts.

Protocol Deviations

Protocol deviations will be entered in the study's Tracking Database are known to happen in order to compile an electronic log for reporting purposes.

Monitoring

Data will be routinely monitored at the time of data collection. REDCap will be used to collect data and the researchers will be prompted at the end of each session to check missing entries. Regular team meetings will be held where researchers can report ongoing data collection concerns to ensure proper adherence to the protocols and high-quality data collection.

Data Collection Instruments

Demographics/Medical Information

Description: Demographic information will be collected via a questionnaire including age, sex, race, ethnicity, marital status, education, and household income. Medical information on smoking, BMI, co-morbidities and all medications will also be collected from the medical record. For both demographic and medical information, the medical record will be reviewed, and discrepancies will be discussed with the Veteran and resolved to facilitate complete and accurate data. These variables will be used to characterize the sample and examine possible influences on treatment response.

Brief Pain Inventory Short Form (BPI-SF)

Outcome Measure: Pain (intensity)

Description: The BPI-SF is a 9-item questionnaire with two subscales (Pain Severity and Pain Interference). (Cleeland & Ryan, 1994). The Pain Severity subscale is being used to evaluate level of pain experienced before and after TKA. Subjects rate their average pain, worst pain and least pain in the past 24 hours and current pain on a 0-10 numeric rating scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine") (Kapstad, Rokne, & Stavem, 2010). Total scores range from 0-40, with higher scores representing more severe pain. The pain severity subscale has demonstrated high internal consistency among patients undergoing joint replacement surgery ($\alpha = 0.91$) (Kapstad, Rokne, & Stavem, 2010). It also has adequate convergent validity with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale among patients with arthritis pain ($r=0.63$) (Mendoza, Mayne, Rublee, & Cleeland, 2006) and patients after joint replacement surgery ($r=0.66$) (Kapstad, Rokne, & Stavem, 2010). The BPI-SF is suitable to be used in randomized controlled trials (RCTs) assessing pain on a daily basis due to its brevity (Mendoza, Mayne, Rublee, & Cleeland, 2006). It has also demonstrated responsiveness to detect changes in pain with physical and psychological interventions for pain (Hwang, Chang, & Kasimis, 2002; Tan et al., 2004). It showed significant changes in pain from baseline to one year following joint replacement surgery, confirming its responsiveness for detecting improvement over time (Kapstad, Rokne, & Stavem, 2010).

Knee Injury and Osteoarthritis Outcome Score (KOOS)

Outcome Measure: Functioning

Description: The KOOS is an extension of WOMAC evaluating short-term and long-term symptom and function in people with knee injury and osteoarthritis. It has 42 items in 5 separately scored subscales: (1) Pain, (2) Other Symptoms, (3) Activity in Daily Living (ADL), (4) Function in sport and Recreation (Sport/Rec), and (5) Knee-related quality of life (QoL). Participants respond using a 5-point scale from no difficulty (0) to extreme difficulty (4) in the last week. Scores are then transformed to a 0-100 scale (0 = extreme knee problems to 100 = no knee problems) (Roos & Lohmander, 2003). For this study, the KOOS ADL and QoL subscales are used as the primary function measures. The KOOS ADL and QoL subscales have demonstrated good test-retest reliability (ICC = 0.89 and 0.84) and internal consistency ($\alpha = 0.92$ and 0.80) in patients with knee OA (Collins et al., 2016). ADL and QoL subscales of KOOS show an adequate convergent validity ($r = 0.65$ and 0.51) with the short form 36 health survey questionnaire (SF-36) physical function subscale in patients with knee OA (Collins et al.,

2016). The KOOS has been sensitive to detect improvement in knee-related functioning following total knee replacement, thus indicating a high degree of responsiveness (Collins et al., 2016; Peer & Lane, 2012) and QoL is the most sensitive subscale to change (Hill & O'Leary, 2012; Roos & Lohmander, 2003).

Pain Catastrophizing Scale (PCS)

Outcome Measure: Pain Catastrophizing

Description: The PCS is a 13-item self-report questionnaire that measures catastrophizing in the context of actual or anticipated pain. The PCS asks participants to rate three domains (magnification, rumination and helplessness) about their experienced pain, on a 5-point scale from (0) not at all to (4) all the time. The PCS total score is used in this study by summing responses to all 13 items for a total score ranging from 0 to 52, with higher scores indicating greater catastrophic thinking. The PCS has good internal consistency (α of total = 0.94) in patients undergoing TKA (Sullivan et al., 2009) and moderate concurrent validity (r = 0.50) with the Tampa Scale for Kinesiophobia, which assesses pain-related fear of movement, in patients before total knee replacement surgery (Sullivan et al., 2009).

Chronic Pain Acceptance Questionnaire Revised (CPAQ-R)

Outcome Measure: Pain Acceptance

Description: CPAQ-R is a 20-item questionnaire that assesses pain acceptance. It includes two subscales, pain willingness (i.e. the willingness to have pain without trying to avoid or reduce it); and activity engagement (i.e. the degree to which one engages in life activities regardless of pain). Each item is scored on a 7-point Likert scale ranging from 0 (never true) to 6 (always true). The measure provides both total score (range from 0 to 120) and two subscale scores (range from 0 to 54, for the 9 item pain willingness subscale; 0 and 66, for the 11 item activity engagement subscale). Higher results indicate higher level of pain acceptance (McCracken, Vowles, & Eccleston, 2004). The two subscales are used for this study and have demonstrated good internal consistency (pain willingness α = 0.78) and activity engagement α = 0.82) among patients with history of chronic pain (McCracken, Vowles, & Eccleston, 2004). Each subscale has adequate discriminant validity (r = -0.63 and -0.51) with the pain-related anxiety subscale of the Pain Anxiety Symptoms Scale (McCracken, Vowles, & Eccleston, 2004).

Chronic Pain Values Inventory (CPVI)

Outcome Measure: Engagement in Values-Based Behavior

Description: The 12-item CPVI is used to measure engagement in values-based behavior. It determines which values are important to an individual and assesses the degree of success they are having engaging in these values. The following six values are included: family, intimate relations, friends, work, health, and growth or learning (McCracken & Yang, 2006). Patients are asked to report the importance of each value on a scale from 0 (not at all important) to 5 (extremely important). Then, they are asked to rate their level of success at living according to each value in the past two weeks on a scale from 0 (not at all successful) to 5 (extremely successful) (McCracken and Vowles, 2008). Two subscale scores are obtained: Mean Success and Mean Discrepancy. The average of the 6 success ratings is used to determine the Mean Success subscale with scores ranging from 0-5. The Mean Discrepancy subscale is calculated by taking the difference between the importance rating and the success rating and then averaging these scores for subscale scores ranging from 0-5. (McCracken & Yang, 2006). Lower average success can represent suffering in living, while higher average success is associated with improved concurrent and future functioning (McCracken & Yang, 2006; Vowles,

McCracken, & O'Brien, 2011). CPVI demonstrated good internal consistencies (α = 0.82) for both the mean success and mean discrepancy subscales among patients with chronic pain (McCracken & Yang, 2006). Acceptable convergent validities have also been shown with the activity engagement subscale of the CPAQ for both the mean success and mean discrepancy subscales in patients with chronic pain (r = 0.62 and 0.54, respectively) (McCracken & Yang, 2006).

Pain Management Strategies Survey (PMSS)

Outcome Measure: Pain Management Strategies

Description: The PMSS is a survey questionnaire to assess the use and perceived helpfulness of medical, complementary, and self-care strategies used to manage pain (Kemp, Ersek, & Turner, 2005). The 42-item PMSS developed by Kemp et al.(2005) was adapted and 10 items were added to assess the effectiveness of other types of pain medication and illicit substances that were not included in the Kemp et al. questionnaire. Participants are asked to indicate whether they have used each strategy in the past year (baseline) or since surgery (postop) and whether they are using the strategy currently (yes/no).. If "yes", they are asked to rate the strategy's helpfulness on a scale of 0 = "not at all helpful" to 4 = "extremely helpful." Participants are also provided space to add any therapies received for pain beyond the strategies listed. It has established content validity (Kung, Gibson, & Helme, 2000) and has been found to provide helpful insights regarding pain management strategies in older adults with persistent pain (Kemp, Ersek, & Turner, 2005).

Depression Anxiety and Stress Scale (DASS-21)

Outcome Measure: Distress

Description: The DASS is a self-report scale to measure the negative emotional states of depression, anxiety and stress. It contains 21 items, 7 items per subscale (depression, anxiety and stress) (Lovibond & Lovibond, 1995). Participants are asked to rate the extent to which they have experienced each state over the past week with a 4-point scale (from 0 = did not apply to me at all to 3 = applied to me very much). Scores are summed per subscale and then multiplied by 2 for possible scores on each subscale ranging from 0 to 42 (Lovibond & Lovibond, 1995). Higher scores indicate more severe symptoms of depression, anxiety and stress. Internal consistency of the DASS-21 subscales in a non-psychiatric sample were high (0.88 for Depression, 0.83 for Anxiety, and 0.85 for Stress) (Osman et al., 2012). Depression, Anxiety and Stress subscales also showed adequate convergent validity (r = 0.55, 0.44, and 0.61, respectively) with Affective Distress subscale of the Multidimensional Pain Inventory and adequate discriminant validity (r = -0.67, -0.50, and -0.63, respectively) with Mental Health subscale of the SF-36 in elderly patients with persistent pain (Wood et al., 2010).

Telephone Administration of the Memory Impairment Screen (MIS-T)

Outcome Measure: Memory Impairment

Description: The MIS-T is a telephone version of the well-validated in-person Memory Impairment Screen (MIS) as a screening test for dementia. The telephone interviewer presents 2 (of 4) target words and asks participants to repeat the words to ensure that they were heard correctly. The interviewer then demonstrates a category cue associated with one of the target words. The participants are asked to choose the word that matches the category cue. The interview then demonstrates the category cue for the other word and this procedure is repeated for the other two target words. After a several minute interference period with no semantic tasks,

participants are asked to free recall the target words. For each target word not freely recalled, the interviewer demonstrates the appropriate category cue to elicit a cued recall. The total MIS-T score is calculated by doubling the number of items retrieved during free recall and adding the number of items retrieved during cued recall and ranges from 0 to 8 (Lipton et al., 2003). The cut point that optimizes classification of dementia for the MIS-T is 4. A cut point of 4, which is used for this study, has shown appropriate sensitivity (78%) and specificity (93%) in healthy older adults (Lipton et al., 2003).

The Drug Abuse Screening Test (DAST)

The DAST-10 is a 10-item self-report questionnaire that measures problematic substance use. The DAST has been found to be a sensitive screening tool for the abuse of drugs other than alcohol (Yudko, Lozhkina & Fouts, 2007). Responses to the DAST-10 are given as binary (yes/no) items. It is scored by adding the number of "yes" responses (except item 3 which is scored 1 for "no" response), yielding a total score that can range from 0 to 10. A high score indicates a severe level of problems related to drug abuse (Skinner, 1982). The DAST-10 has presented a high internal consistency and test-retest reliability ($r = 0.90$ and $\alpha = 0.90$) in adults including drug abusers and non-abusers (Bedregal, Sobell, Sobell, & Simco, 2005). It also has strong convergent validity ($r = 0.87$) with the Reduce Annoyed Guilty Start test in adults including drug abusers and non-abusers (Bedregal, Sobell, Sobell, & Simco, 2005).

Cut down, Annoyed, Guilty, and Eye-opener (CAGE)

The CAGE is a 4-item self-report questionnaire to screen alcohol abuse or alcohol dependence. The participant responds yes/no to 4 questions. Each item is scored 1 if the participant answers "yes" and 0 if the participant answers "no." The total score can range from 0 to 4 (Ewing, 1984). The cutoff for CAGE is traditionally 1 or 2 to detect alcohol abuse or dependence (Teitelbaum & Carey, 2000). The CAGE has established test-retest reliability ($r = 0.95$) in people with alcohol use disorders (Teitelbaum & Carey, 2000) and internal consistency ($\alpha = 0.78$) in a sample of people both with and without alcoholism (Meneses-Gaya et al., 2010). It also has a good convergent validity ($r = 0.77$) with the Alcohol Use Disorders Identification Test in a sample of people both with and without alcoholism (Meneses-Gaya et al., 2010).

PTSD Checklist – short version (PCL-5)

The PCL-5 is a 20-item self-report questionnaire to assess post-traumatic stress disorder (PTSD). Each item is rated on a 5-point scale with anchors from "not at all" to "extremely" indicating how much the participant has been bothered by the PTSD symptoms in the past month. A total symptom severity score can be obtained by summing the scores for a range of scores from 0 to 80. A higher total score demonstrates more severe PTSD symptoms (Bovin et al., 2016). The PCL-5 has been validated with a high internal consistency in war veterans ($\alpha = 0.95$) (Pietrzak et al., 2015) and good test-retest reliability in veterans ($r = 0.86$) (Bovin et al., 2016). It also had strong convergent validity with the Patient Health Questionnaire(PHQ)-depression ($r = 0.74$), the PHQ-generalized anxiety disorder ($r = 0.67$), the PTSD Symptom Scale ($r = 0.68$), the Beck Anxiety Inventory ($r = 0.61$), and the Beck Depression Inventory ($r = 0.64$) in veterans (Bovin et al., 2016; Wortmann et al., 2016).

Data and Safety Monitoring (DSM) Plan

Monitoring Entity, Roles and Responsibilities

Data and safety monitoring will be conducted by a Safety Monitoring Committee (SMC) made up of three faculty independent of the protocol (one at the Baylor College of Medicine/DeBakey VA Medical Center and two at the University of Iowa). This committee will convene annually to provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. Members of the SMC include:

1) Dr. Ricardo Jorge, MD, Professor, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Associate Director Brain Injury Medicine Program at the Beth K. and Stuart C Yudofsky Division of Neuropsychiatry, Houston, TX and Director, Translational Research Center for TBI and Stress Related Disorders (TRACTS- Houston) Michael E DeBakey VA Medical Center, Houston, TX;

2) Dr. James Torner, Professor in Epidemiology at the University of Iowa (biostatistics expertise); and

3) Dr. Ann Marie McCarthy, Professor and Associate Dean for Research and Scholarship in the College of Nursing at the University of Iowa.

These faculty are all familiar with the process and goals of this review.

Roles of the SMC

1. Protect participants from exposure to unreasonable or unnecessary research risks by monitoring the trial data for effectiveness and safety.
2. Monitor study progress and conduct.
3. Review interim data in the context of the most recent scientific literature and access unmasked data if necessary.
4. Ensure that the study does not continue beyond the point when objectives have been met and a clinically meaningful answer of importance to the scientific community and the public has been obtained.

Responsibilities of the SMC

1. Approve study protocols and plan for data and safety monitoring.
2. Establish and approve reporting guidelines for unanticipated events.
3. Review unanticipated events and make recommendations as appropriate to needed changes in research protocols, the informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.
4. Review recruitment and retention data.
5. Review interim analysis of outcome data for early evidence of efficacy, lack of efficacy, or evidence of study futility.
6. Review published reports of related studies submitted by the study investigators, or SMC members to determine whether the monitored study needs to be changed or terminated.
7. Review the proposed stopping guidelines as specified in the protocol and, at its discretion, recommend modification to the proposed plan, or propose a plan, if none has been proposed.

Meetings of the SMC

The focus of the **open** session of each meeting is on the general conduct and progress of the study. Specifically, the focus of the open session is: unanticipated events, subject accrual, protocol compliance, site performance, quality control, and timeliness and completeness of follow-up. During this time, no confidential data will be discussed and the blind will be maintained. The PI and other appropriate study leadership and the protocol specific biostatistician should be in attendance in order to present results and respond to questions.

The focus of the **closed** session of each meeting will be on grouped safety data and, if appropriate, efficacy data to include unmasking of blinded data presented by the protocol specific statistician(s).

Recommendations will be made to continue the study as planned, to make adjustments to the study plan, suspend or to terminate the study during the **executive** session, attended only by the SMC members.

The co-PIs will:

1. Schedule the meetings of the SMC and draft the agendas (to be approved by the SMC).
2. Ensure meeting materials are distributed to each SMC member prior to meetings and in sufficient time to permit adequate review.
3. Amend the protocols/consent documents in accordance with SMC recommendations, if applicable.
4. Submit final meeting minutes and summaries to NINR within 20 business days following each SMC meeting.

Procedures for monitoring study safety, minimizing research-associated risk and protecting confidentiality of participant data

<u>Monitoring study safety</u>

In addition to the SMC annual meetings to provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data, the research team will comply with all IRB procedures and auditing, including auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance/annual trainings.

<u>Minimizing research-associated risk</u>

Detailed operational protocols will be developed which incorporate steps to minimize risks. The multi-PIs and Project Directors will attend data collection sessions at their site regularly to ensure that the protocols are followed. All appropriate guidelines will be followed, including the use of Informed Consent and using the protocol and forms approved for use by the IRB. If during the course of the study any member of the research team detects or becomes aware of any unanticipated events or safety concerns during their contacts with the subjects, she/he will immediately inform the PI at the respective site. If not available, the team will contact Co-Facilitators; Hadlandsmyth (Iowa) or Smith (Houston).

Minimizing Risk Associated with Suicidal Ideation and Psychological Distress

Upon enrollment, all participants will be provided with the phone number of the local VAMC's Suicide Prevention Coordinator as well as the Veteran crisis hotline. If at any time during participation in study assessments, the workshop or "booster" session a participant indicates suicidal ideation, a research team member will ask 3 follow-up questions as indicated by the Suicide Risk Protocol. If these follow up questions suggest that suicide is imminent (i.e., the participant answers 'yes' or 'maybe' to question 3 of the Suicide Risk Assessment or describes a detailed plan to kill him/herself on a specific date in the immediate future), emergency services will be utilized as per the protocol detailed in the "Suicide Risk Management" document. In addition, patients with imminent risk of suicide, attempts of suicide, incidents of violence toward others, or psychiatric hospitalizations will lead to withdrawal from the research protocol and will be reported to the SMC, institutional IRB and NINR.

Protecting Confidentiality of Participant Data

A number of precautions will be undertaken in order to protect the confidentiality of study participants. All documents containing identifying information (e.g. consent forms, patient correspondence) will be kept separate from the participant's main data file at each site. The main data file will contain only study identifier numbers. A separate key that links the two sets of files will be kept by the study coordinator in a separate locked file. All data will be locked in the research offices of the PIs and study site coordinators. The PIs will have a shared electronic folder in order to share information. Only the PIs and key research staff will have access to this electronic folder. The computers on which data are entered will also be kept in the locked research offices; access to the computers is password-protected. Computer data will be entered by subject code only (without identifying information). The codes will be kept in a locked safe or a password-protected database, in an encrypted computer behind the VA firewall. No subject will be identified by name in any report of the study. Data will be kept confidential and will not be released to the general public. Data will be available to research staff, institutional IRB's and government agencies as required.

To protect participant confidentiality in the small-group discussions, participants will be reminded at the beginning of small-group discussions not to bring up personal information that they would not want disclosed to others, and they will be asked not to discuss details of the group discussion with anyone outside the group. During small-group discussions, the facilitator will be mindful of potential breaches of confidentiality or personal revelations that might prove harmful, remind participants of the confidentiality rules and stop discussions if appropriate.

Procedures for Identifying, Reviewing, and Reporting Unanticipated Events

An unanticipated problem involving risks to subjects or others is any event or problem that:

1) was unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document and the characteristics of the subject population being studied; AND

2) was related or possibly related to participation in the research (possibly related means

there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in the research); AND

3) suggests that the research places subjects or others (those not directly involved in the research such as research staff or family members) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Examples of unanticipated events involving risks to subjects or others include, but are not limited to:

1) a breach of confidentiality

2) a subject complaint when the complaint indicates unexpected risks or cannot be resolved by the investigators,

3) a research team member experiences harm in the conduct of the study,

4) a new risk of the study procedure is identified by an outside source (sponsor, federal regulatory agency, outside site, etc.)

All unanticipated events shall be reported to the co-PIs and both site directors, the SMC, institutional IRBs and NINR within 5 working days of their occurrence. They will also be recorded in a shared database which will be reviewed at the monthly meetings of the Steering Committee and yearly meetings of the SMC. A summary of recommendations made by the SMC in response to any unanticipated event, as well as notice of any actions taken by the IRB regarding the research and any responses to those actions, shall also be reported to NINR within 5 working days.

Compliance across Sites

Procedures to ensure compliance with the monitoring plan and reporting requirements across sites include:

1. All meetings of the SMC shall also be attended by the co-PIs and project directors at each site and the project biostatistician (Zimmerman).
2. All communications from the SMC shall be sent to the co-PIs and project directors at each site.
3. The reporting procedure for unanticipated events shall be documented in a common Manual of Operations.
4. Changes to study procedures proposed and approved by the SMC shall be announced at the monthly Steering Committee meetings and the common Manual of Operations updated accordingly.
5. All screening, outcome, and unanticipated event data shall be stored in common databases. All data requested by the SMC or NINR shall be compiled from these databases by the senior project coordinator, reviewed by the project coordinator at the other site/s, and approved by the co-PIs.

<u>Assessment of External Factors or Relevant Information</u>

Published reports of related studies will be monitored by the study investigators or SMC members through PubMed searches and attendance at scientific meetings prior to SMC meetings. These reports

will be submitted for review prior to annual SMC meetings, or as needed, to determine whether the monitored study needs to be changed or terminated.

Interim Analyses

An interim analysis of outcome data for early evidence of efficacy, lack of efficacy, or evidence of study futility will be performed at the discretion of the SMC. These data will be reviewed at the SMC closed meeting, as appropriate.

Study Completion and Closeout Procedures

Study closeout activities are performed to confirm that the site investigator's study obligations have been met and post-study obligations are understood.

The project coordinator in conjunction with the steering committee will determine when data collection is complete based on when the anticipated number of participants in each study group have been completed (ACT, AC). A final decision on data collection will be initiated by the study coordinator and brought to the steering committee for final approval. This will be based on achieving an adequate number of subjects per group (150 per group) who have completed all data collection.

Upon completion of the study, the project coordinator and the primary investigators at University of Iowa and Baylor University will notify the appropriate IRB at each institution, the study team, SMC, NINR, and clinical trials.gov of trial completion. This will involve a modification to the IRB, and a written letter to the study team, SMC, NINR and changing the status on clinical trials.gov online.

Study files will be archived and stored in the study's shared file on the VA server and in the study's file on the University of Iowa server. These will then be made available as needed for external audits.