COVER PAGE

Pre-op Cognitive Behavior Therapy to Decrease Chronic Post-Surgical Pain in TKA

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PROTOCOL TITLE: Pre-op CBT to Reduce the Risk for Development of Chronic Post-surgical Pain in Patients undergoing Total Knee Arthroplasty

INTRODUCTION AND PURPOSE:

A significant number of patients develop chronic post-surgical pain following knee joint replacement surgery, and the risk factors for this problematic outcome have been identified. Proposed is the development and preliminary efficacy testing of a novel computer-assisted cognitive behavioral intervention integrating opioid taper delivered in the four weeks prior to surgery to address these risk factors, with the expectation that both the severity of post-operative pain and the subsequent incidence of chronic post-surgical pain will be reduced. In that chronic post-surgical pain brings with it diminished functionality and quality of life, ongoing opioid use, and direct patient costs, it is it is critical that interventions aimed at mitigating its development are implemented and evaluated in the clinical setting.

OBJECTIVES:

In a sample of adult men and women with chronic pain, on opioid therapy and undergoing a planned TKA, the objectives of this randomized clinical trial are to:

1. Add a motivational interviewing component to a validated computer-assisted CBT intervention for chronic pain (PAINTrainer) to encourage opioid tapering in the 4 weeks prior to surgery.
2. Describe the efficacy of the 4-week targeted pre-operative CBT intervention in 75 TKA patients to decrease preoperative chronic pain severity, preoperative opioid consumption, and symptoms of depression, anxiety and pain catastrophizing prior to surgery in comparison to 75 TKA patients randomized to treatment-as-usual.
3. Describe the effects of a 4-week targeted pre-operative CBT intervention in 75 TKA patients on 72hr post-operative pain severity, and 3- and 6-month rates of CPSP in comparison to 75 TKA patients randomized to treatment-as-usual.

BACKGROUND:

Knee Joint Replacement and Chronic Post-surgical Pain

Total knee arthroplasty (TKA) is among the most common surgical procedures performed in the US[1,2], and as the population ages and face age-related joint deterioration, will only increase in frequency.[3,4] Although in the majority of cases, patient-centered outcomes (pain, function and quality of life) are improved following this procedure, a significant number of patients develop chronic post-surgical pain (CPSP), which is often rated as severe, and includes treatment-resistant neuropathic components.[5] The International Association for the Study of Pain defines CPSP as pain that develops or increases in intensity after a surgical procedure, persists beyond the tissue healing process (> 3months), and is localized to the surgical field or innervation territory of nerve located in surgical field.[24] Rates of CPSP are alarmingly high following TKA, with Petersen and colleagues [6,7] reporting that between 44% to 53% patients develop CPSP,15% to 19% of whom rate their pain as severe. Clearly, the development of CPSP following TKA is a significant adverse outcome, which brings with it decreased quality of life, diminished functionality, disability, and perhaps most concerning in the era of the opioid crisis, long-term opioid use.[8,12] Further, CPSP is associated with notable economic burden, with recent analysis suggesting almost $30,000 in annual adjusted indirect costs to patients per year, an amount directly related to the severity of CPSP pain.[13]

Preoperative Predictors of Chronic Post-surgical Pain

The etiology of CPSP has been described as multifactorial, and attributed to the inevitable nerve damage (both directly to nerve and to innervated tissues) and the concomitant release of inflammatory mediators which accompany the surgical procedure. The nociceptive “afferent barrage” associated with the incision and tissue manipulation result in both central sensitization of nociceptive systems and centralization of pain in brain systems[15,18,25], theorized to lay the foundation for pain chronification. However, not all patients undergoing surgery will develop CPSP; predictors include factors in cognitive-affective, sociodemographic, genetic, and environmental domains.[10,15] Most consistently identified as preoperative risk factors for the development of CPSP are, (1) the presence of pain in the body part to be operated on or elsewhere[9,14,16], (2) chronic opioid use[10,11,15,18,26], and (3) symptoms of psychological distress including depression, anxiety, or pain catastrophizing.[9,14,16] In fact, predictive evaluations show that the presence of preoperative pain increases the odds of developing 6-month CPSP 2.8 to 4.3 fold, and preoperative distress increases the odds by 3.4.[16] Acknowledging the role preoperative opioid use plays in the development of CPSP, clinical experts are calling for preoperative opioid tapering as an approach to improve post-operative pain outcomes.[27]

In addition to these preoperative risk factors, the severity of post-operative pain has been identified as an independent predictor of the development of CPSP.[9] Arguments have been made for each of the identified pre-operative risk factors amplifying post-operative pain severity, in that pre-existing pain brings with it inflammatory and sensitization elements, and antecedent distress results in the patient less able to cope with discomfort. Perhaps most compelling is the role long-term opioid use plays in post-operative pain severity; related to the putative effects of opioid-induced hyperalgesia (OIH),[28,29] the patient arrives to the surgical setting with opioid-derived increased sensitivity to pain, which becomes evident during the post-operative pain experience. Figure 1 explicates the relationships among these risk factors and the development of CPSP.

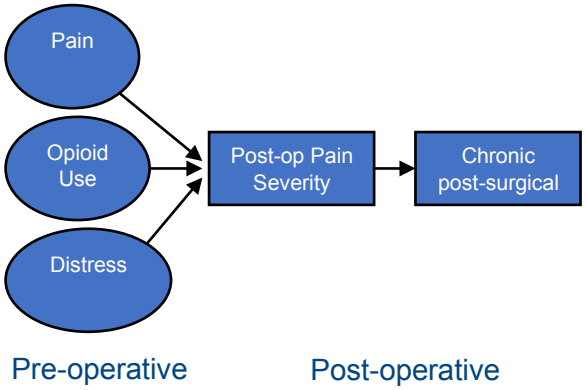

Figure 1. Predictive factors of CPSP following TKA

Cognitive-Behavioral Therapy for Chronic Pain

A mainstay of multi-modal treatment for chronic pain is cognitive-behavioral therapy (CBT). CBT is a structured psychosocial intervention that aims to change maladaptive thoughts, behaviors and beliefs about pain and disability, improve emotional responses to these, and cultivate coping and adjustment strategies to manage distress and discomfort.[30,31] Multiple integrative and systematic reviews support the efficacy of CBT-based interventions to decrease chronic pain severity, improve physical function and decrease problematic thought patterns, including pain catastrophizing and fear avoidance beliefs.[32,33,35-38] More recently, the efficacy of CBT delivered in online platforms has been established and demonstrated to be comparable to outcomes with in-person delivery[32,34,40], greatly expanding the number of patients with chronic pain who benefit from the intervention. Notably, across these reviews, the quality of studies has been graded as adequate[33,36] to high,[37,38] with the low risk for bias across the majority of bias sources,[34,35,38] and no evidence for publication bias when assessed.[36,38] A particularly promising internet-based CBT pain program for the population of interest, PAINTrainer[41], demonstrated improved pain, function, coping and global health in patients with chronic knee arthritic pain in comparison to an internet education control, with benefits persisting for up to 52 weeks.[42,43]

Cognitive-Behavioral Therapy for the Preoperative Setting

As described above, internet-based CBT has proved effective for patients suffering lower joint chronic pain, however it has been primarily delivered in post-operative or primary care settings, not preoperatively to improve surgical pain outcomes. Evidence from bariatric surgery populations suggest that benefits associated with preoperative CBT include decreased problematic eating behaviors and affective distress following surgery (pain outcomes not examined).[44,45] Much of the work in preoperative interventions for TKA focus on physical rehabilitation,[46] as opposed to targeting chronic pain symptoms, opioid therapy and distress, which may explain findings of only slight and short-term improvements in early postoperative pain and function.[47] Only two reports testing CBT-based interventions prior to TKA could be found in the literature (one feasibility trial[48] and one randomized clinical trial[21]), and both focused only on managing symptoms of distress (depression, anxiety, catastrophizing); neither considered the roles of preoperative pain, opioid consumption or post-operative pain severity in predicting longer term outcomes (pain, long-term opioid use, functionality).

CHARACTERISTICS OF THE STUDY POPULATION:

1. Target Population and Accrual:

A total of 150 male and female chronic pain patients on opioid therapy seeking total knee arthroscopy (TKA) at the Penn Presbyterian Medical Center will be included in the study sample, half of whom will be randomly assigned to receive the targeted computer-assisted CBT intervention beginning 4 weeks prior to their planned TKA surgery; as the control condition, the others will receive treatment-as-usual, consisting of a mandatory four-hour educational session.

A power analysis was conducted for the post-operative pain outcomes; being a novel intervention, opioid taper outcomes were not considered. Estimated group means, variances, and effect-size were drawn from the literature.[41,42] The sample size estimate was derived for the primary outcome variable, chronic pain severity, using an expected baseline mean of 4.82 (Effect size: 0.33). Based on estimates obtained, a sample size of 75 participants provides 80% power to detect a pre-post improvement in pain severity (14.5%), depression (21.3%), anxiety (24.3%), and catastrophizing (29.5%), statistically significant at alpha of 0.05. Being a novel intervention, the analysis for chronic post-surgical pain will be considered exploratory and used to obtain effect size estimates. We anticipate a low attrition rate (10%) and will over-recruit 16 additional participants (total 83 subjects per group) to retain adequate power.

2. Key Inclusion Criteria:

1. Males and females, age > 21 years
2. Chronic non-malignant pain of at least 3 months duration
3. Morphine equivalent daily dose (MEDD) > 50 milligrams for at least 3 months
4. Able to enroll at least 4 weeks prior to planned surgery
5. Able to speak, read and comprehend in English at the 6th grade or higher proficiency

Participants will be selected so as to represent the gender, ethnicity, and age of the patient population of individuals seeking TKA in greater Philadelphia area, thus the sample is expected to be 50% women, 55% white, 35% African-American, 6-8% Latino, and 2-4% other or multiracial, and on average 67 years of age. No restrictions on gender or ethnicity will be applied. Because total knee arthroplasty surgery is uncommon in children, individuals under the age of 21 will not be included in this proposed study.

3.Key Exclusion Criteria:

1. Pain of malignant origin
2. Current or past history of opioid use disorder (including those on medication-assisted therapy)
3. Revision of TKA
4. Comorbid CNS disease such as dementia, HIV, psychosis, poorly controlled bipolar disorder or any condition interfering with informed consent

Pain of malignant origin is likely to worsen with disease progression over time, thus the efficacy of the intervention on pain outcomes would be limited. Similarly, opioid use in patients with opioid use disorder is motivated by factors other than pain, thus opioid use outcomes would be spurious if these patients were included in the analysis. Finally, surgical outcomes for patients undergoing a revision of their TKA have poorer pain and functional outcomes, introducing known variance to the efficacy of the intervention; excluding them from the sample preserves homogeneity as required for a small pilot study.

4. Subject Recruitment and Screening:

Participants will be recruited from those preparing to undergo total knee arthroplasty (TKA) surgery at the large and nationally-renowned Participants will be recruited from those treated at the large and nationally-renowned Department of Orthopedic Surgery at the Penn Presbyterian Medical Center. The Center performs approximately 1100 major TKAs per year with an estimated 20-30% of patients who have been taking opioids regularly for at least 3 months for the treatment of a chronic nonmalignant pain condition.

The EHR of all patients scheduled for TKA at least 5 weeks in the future will be examined to identify those meeting inclusion criteria. Eligibility will be reviewed by Co-I Elkassabany; those eligible will be contacted by the study coordinator to inform them about the study. Those who express interest will be scheduled for a screening visit during which informed consent will be obtained in a Center private room.

If a patient assigned to standard treatment requests the enhanced treatment, he or she will be removed from the study.

5. Early Withdrawal of Subjects:

Subjects may be withdrawn from the study prior the expected completion of the project if there are concerns about the safety of the subject, failure of subject to return for visits, failure to locate the subject and if subjects withdraw their consent. Concerns about safety include feelings of extreme anxiety or depression which will be evaluated by co-PI Cheatle.

Subjects are also informed via the informed consent process that they are free to leave the study at any time, and that withdrawal will not interfere with their future care.

6. Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

7. Populations vulnerable to undue influence or coercion:

The population from which the sample will be recruited are not vulnerable to coercion or undue influence.

STUDY DESIGN:
A randomized clinical trial is proposed to evaluate the efficacy of the novel computer-assisted preoperative CBT/opioid sparing intervention to affect acute and chronic post-operative pain outcomes. Specifically, 150 male and female patients meeting study inclusion criteria and preparing to undergo TKA at the Penn Presbyterian Medical Center will be randomized to either receive the computer-assisted preoperative CBT intervention (n=75) or treatment-as-usual (control, n=75). The effectiveness of the intervention to address the preoperative risk factors for CPSP will be evaluated by comparing pain severity, opioid use, symptoms of depression, anxiety and pain catastrophizing before and following the 4-week pre-surgical period and compared within and across subjects. Post-operative pain severity will be abstracted from the electronic health record (EHR) and compared to post-operative pain severity ratings between the intervention and control groups. Similarly, group differences will be inspected for rates of CPSP at 3- and 6-months following surgery. In addition, due to the novelty of the CBT/opioid sparing intervention, brief (15-20min) qualitative interviews will be conducted with the participants who received it during the study visit immediately prior to surgery, to assess patient utilization, and satisfaction with the program in general, and the opioid taper component specifically; adherence is tracked by the PAINTrainer. Participants will be prompted to comment on the perceived ease of use, burden, helpfulness and quality of the CBT intervention.

A randomized clinical trial was designed because it provides the highest level of evidence and lowest risk for bias. The methods employed are predominantly quantitative, although a qualitative survey approach is used to assess subject satisfaction with the intervention. The project is designed, staffed and budgeted to be completed in 24 months. In consultation with consultants, Dr. Cheatle will train the study coordinator coach on delivering the opioid taper intervention during months 1-3, during which time study start-up activities will take place. Enrollment will begin month 3; at a rate of 12-13 enrollments per month, we anticipate having enrolled 166 subjects (n=150, assuming 10% attrition) by study month 15, providing adequate time for 3- and 6-month follow up, and dissemination activities.

The research will be conducted in the Department of Orthopaedic Surgery at Penn Presbyterian Medical Center, and data analysis will be performed at the Biostatistics * Evaluation * Collaboration * Consultation * Analysis (BECCA) lab at the U Penn School of Nursing.

The duration of subject participation is approximately seven (7) months beginning four (4) weeks prior to surgery and ending following the 6-month data collection time point. The baseline study session will last approximately 30minutes for those in the control group and 60minutes for those in the experimental group. For those in the experimental group, subjects will spend approximately nine (9) hours prior to surgery receiving the intervention. For those in the control group, subjects will spend approximately four (4) hours prior to surgery receiving the standard educational care. Just prior to the surgery, subjects in both groups spend approximately 45minutes providing pre-operative data, and they will additionally spend one (1) hour providing data at the 3- and 6-month follow up at 30minutes each. Thus, the duration of participation for those in the experimental group is approximately 12 hours, and for those in the control group, approximately 7.5 hours.

METHODS:

1. Study Instruments:
Preoperative chronic pain – The severity of preoperative chronic pain will be evaluated with the Brief Pain Inventory (BPI),[52] along two dimensions: intensity and interference. Pain intensity is rated on a 0 (no pain) to 10 (worst pain imaginable) scale as the worst in the past 24 hours, least in the past 24 hours, average pain and current pain. Pain interference is measured in 7 areas: general activity, mood, walking ability, work, sleep, enjoyment of life and relationships on a 0 (no interference) to 10 (interferes completely) scale. The composite mean of these scores are used as a pain interference score. BPI scores will be collected prior to the intervention and compared to those collected just prior to surgery and at 3- and 6-month follow-up.

Long-term opioid use – Preoperative opioid use will be measured by converting to morphine equivalent daily dose (MEDD) prior to beginning the intervention, during the study visit just prior to surgery and at the 3 and 6 months follow up if the patients are still taking opioids. At each timepoint, state prescription drug monitoring program will be queried as a check on self-reported opioid use.

Pain catastrophizing – Pain catastrophizing will be measured by the Pain Catastrophizing Scale (PCS).[53] The PCS is a 13-item self-report scale, with each item rated on a 5-point scale: 0 (Not at all) to 4 (all the time). It is broken into three subscales (magnification, rumination, and helplessness); results from the initial development and validation studies indicate that the PCS is a reliable and valid measurement tool for catastrophizing in clinical and non-clinical populations. PCS will be completed prior to and following completion of the intervention and at the 3- and 6-month follow ups to assess the durability of the intervention.

Depression and Anxiety - To measure symptoms of depression and anxiety, the PROMIS® (Patient-Reported Outcomes Measurement Information System) person-centered measures will be utilized.[54] Specifically, the 8-item PROMIS depression and anxiety short forms will be compared prior to and following completion of the intervention; to evaluate the stability of CBT skills, the PROMIS will also be administered at 3 and 6 months.

Potential confounders – Pre-existing medical comorbidities or post-operative complications may affect surgical outcomes with respect to pain severity and resolution. To account for the effects of these confounders, all medical comorbidities will be extracted from the EHR by the study coordinator prior to surgery and recorded in the study database. Also added to the study database will be any unanticipated adverse events following surgery, and with medical comorbidities, considered as moderators of the effects of the intervention on the development of CPSP.

Post-operative pain intensity – Severity of post-operative pain will be operationalized as (1) responses on a visual analogue pain scale (VAS) and (2) consumption of opioid analgesic medications during the first 72 hours following surgery. The VAS ranges from 0 (no pain) to 10 (worst pain imaginable), and pain scores are collected every 4 hours as part of routine practice. Pain ratings will be graphed over time and area under the curve calculated. Dose of opioid analgesics consumed during this period (24hr increments and total) will be abstracted from the electronic health record and converted into MEDD for analysis.

Chronic post-surgical pain – To evaluate for the presence of CPSP, subjects will be asked at 3- and 6-months if they have pain in the surgical site that developed or increased in intensity following the surgery utilizing a checklist based upon the IASP definition of CPSP (Appendix). If they respond affirmatively, BPI pain scores will be collected to assess the intensity and interference associated with the CPSP. In addition, subjects will be asked if they are continuing to use opioids at these timepoints, and if so, daily MEDD calculated for analysis.

2. Group Modifications:

The only group modification with respect to measures is that only those in the intervention group will participate in the survey assessing subject satisfaction with the intervention.

3. Method for Assigning Subjects to Groups:

A randomization scheme will be generated by the study biostatistician and provided to the study coordinator who will assign consecutively enrolled subjects to group.

4. Administration of Surveys and/or Process:

The data collection schedule is described below:

	Baseline (T-4weeks)	Pre-operation (T0)	Post-operation (T = 72hr)	Follow-up (T + 3 and 6 months)
Chronic Pain Intensity (BPI)	X	X		X
Opioid Use (MEDD)	X	X		X
PDMP review	X			X
Pain Catastrophizing (PCS)	X	X		X
Depression & Anxiety symptoms (PROMIS)	X	X		X
CBT use, adherence, satisfaction[a]		X		
Post-operative Pain Severity (72hr VAS)			X	
Post-operative Pain Severity (72hr MEDD)			X	
Chronic post-surgical pain checklist				X

[a] subjects in treatment group only

5. Data Management:
Collected data will be entered into the U Penn School of Nursing REDCap (Research Electronic Data Capture) system by trained CITI- and HIPAA-certified research assistants, which is a central and secure resource for data processing and management. As the front-end collection instrument is created, REDCap automatically creates a database designed to store the data that will be recorded from the research. The U Penn School of Nursing has licensed its own version of REDCap that is housed on password protected servers located within a data center inside the School of Nursing firewall, and therefore are afforded the same network protections as other sensitive clinical systems. REDCap was developed specifically around HIPAA-Security guidelines with features such as data encryption and is recommended to Penn researchers by our Office of Human Research.

Data quality will be monitored by random inspection of the completed datasets by the study coordinator and any problems detected will be discussed with the co-PIs. In addition, the PIs will carefully monitor the data accrual weekly. Data will be entered on an ongoing basis under the direction of the study coordinator, and weekly reports detailing health events, study progress, and data accuracy and completeness will be generated for review by the PIs and co-investigators. Quality assurance activities will be supervised by the study coordinator. Prior to analysis, missing data or discrepancies will be corrected by the project director based on source documents. The study's statistician will analyze the data, using SAS for Windows Version 9.4 statistical software.

Data monitoring of all aspects of this study will proceed in an exacting manner and meet all IRB requirements. Data will be collected by trained research staff using standardized hardcopy and electronic forms and will only be identified with a study ID. Personal identifiers required for follow-up will be linked with the study ID and kept confidential by Drs. Cheatle and Compton in a secured cabinet. No presentation or publication of the results of this study will refer to the individual participants or present information that would identify any participant. No data will be disclosed to personnel not listed on the study protocol.

6. Subject Follow-up:
Using contact information obtained at the baseline visit, subjects will be contacted via telephone at 3- and 6-months following surgery to determine if CPSP is present utilizing a checklist based upon the IASP definition of CPSP (Appendix). If present, the BPI will be administered, and any opioid use recorded and checked against the PDMP. In addition, the PCS and PROMIS measures will be collected to evaluate the durability of CBT training effects. The sample does not include transient groups, minimizing potential attrition.

STUDY PROCEDURES:

1. Detailed Description:
The study procedures, including all the visits, contacts, and interactions are described sequentially below:

Recruitment and Consent: The EHR of all patients scheduled for TKA at least 5 weeks in the future will be examined to identify those meeting inclusion criteria. Eligibility will be reviewed by Co-I Elkassabany; those eligible will be contacted by the study coordinator to inform them about the study. Those who express interest will be scheduled for a screening visit during which informed consent will be obtained in a Center private room.

Baseline Study Session: Once informed consent is obtained, Baseline measures on the severity of chronic pain, opioid use, pain catastrophizing, and symptoms of depression and anxiety and evidence of OUD will be collected at this time. The PDMP will be consulted to verify self-reported opioid use. In addition, the subjects randomized to the intervention group will be provided access to the computer-assisted preoperative CBT intervention (described below) and trained on its use. It is anticipated this study session will last no longer than 30minutes for those assigned to the control group, and 60 minutes for those assigned to the treatment group.

Pre-operative CBT Intervention: In the current application we will be utilizing and building upon a well-vetted internet-based pain coping skill program (PAINTrainer).[41-43] The PAINTrainer includes 8 sessions, each of which takes 35-45 minutes to complete, and teaches an evidence-based pain coping skill. The program is led by a virtual coach and content is provided in audio to minimize reading and facilitate program completion for fatigued or low literacy patients; only key information is highlighted with brief, large-font onscreen text. Illustrations, animations, interactive exercises, and tailored feedback are used to reinforce learning. The intervention can be delivered on a number of platforms (iPad, smart phone, PC, Mac), and four iPads with internet connectivity will purchased to loan to participants who do not have a device on which to run the application. Users can close a

session before completing it and resume where they left off, and access program resources to manage goals and reminders, log practices, review progress in easy-to-read graphs, read about others' experiences using the skills, and share their own. In addition, they will have access to PAINTrainer for one-month post operatively to reinforce the basic CBT principles; the program also tracks participants' use. Although it is recommended to complete one session per week, in this application patients will be asked to complete 2 sessions per week for four weeks; the developers of the PAINTrainer (consultants Keefe and Rini) note that the efficacy of flexible approaches, including shortening of the delivery schedule.

In addition to the PAINTrainer, we will integrate a motivational interviewing (MI) intervention delivered by a trained "coach" across the sessions about (1) the benefits of opioid tapering for post-operative pain control, (2) approaches for safely tapering, (3) identifying and managing withdrawal symptoms patients may experience. Co-PI Cheatle will provide scripted language and train the study coordinator to effectively deliver this education within the CBT context employing MI techniques, and monitor fidelity to the delivery at regular intervals over the course of the study. The content and tapering guidelines will be based upon the US Department of Veterans Affairs Pain Management Opioid Taper Decision Tool[55] which provides guidance on dose reduction schedules, over-the-counter medications to treat mild withdrawal symptoms, and resources to manage discomfort or distress. Patients will not be expected to taper completely off opioids during the intervention period, but up to 30% reduction in daily opioid dose is anticipated. For future testing, the MI intervention will be integrated into the platform virtual coach, however it is cost-prohibitive to do so in the current application.

Treatment as usual: Patients scheduled to undergo total joint arthroplasty at the study site are automatically enrolled in a mandatory 4-hour education class delivered by a nurse educator or physical therapist. Utilizing an in-person Powerpoint presentation format, patients are informed about pre-habilitation exercises to do prior to surgery; what to expect the day of surgery; the multimodal analgesia protocol used in the perioperative period; options for anesthesia and analgesia; and the expectation of physical therapy after surgery.

Pre-operative study session: Immediately prior to the surgical procedure, patients in the experimental group will meet with the study coordinator and baseline assessments will be repeated. In addition, the subject will be interviewed to gain understanding of their perceived ease, burden, satisfaction and likability of the intervention. It is anticipated that this study session will last no longer than 45 minutes. At the completion of the session, use data from the computer-assisted CBT program will be downloaded and recorded.

Post-operative Pain: Post-operative pain intensity and opioid use (converted to MEDD) data will be extracted from the EHR for the first 72 hours post-operatively. If the patient is discharged prior to 72 hours, he or she will be provided a pain diary to record daily pain ratings and opioid use.

Chronic Post-surgical Pain: Subjects will be contacted via telephone at 3- and 6-months following surgery to determine if CPSP is present utilizing a checklist based upon the IASP definition of CPSP (Appendix). If present, the BPI will be administered, and any opioid use recorded and checked against the PDMP. In addition, the PCS and PROMIS measures will be collected to evaluate the durability of CBT training effects.

2. Data Collection:
Data related to 72-hour post-operative pain and opioid use outcomes will be extracted from the EHR and opioid use data will be validated from PDMP entries; all other data will be sourced directly from the subject. These data are not existing at the time of submission of the IRB application. No tissue specimens will be collected or used in this study.

3. Genetic Testing:
Not applicable.

4. Use of Deception:
Not applicable.

5. Statistical Analysis:
Preliminary analysis of all outcome and baseline demographic variables will describe and test for differences in baseline measures between the groups. Adequacy of randomization will be evaluated by tests of differences between the intervention and usual care groups. These baseline comparisons will be based on t-tests or Wilcoxon rank sum tests for continuous variables, depending on the symmetry of the distributions; on logistic regression for

binary or ordinal variables; and on Poisson log-linear regression for count data. If imbalances are found at baseline, then the relevant variables will be treated as confounders in the post study analyses.

For the second study objective, we expect that participants, who receive a MI intervention along with a validated computer-assisted CBT intervention for chronic pain (PAINTrainer) will demonstrate a significantly greater improvement in outcome variables from baseline vs those receiving usual care. The outcome variables will include change in the severity of pre-operative chronic pain, opioid use, and psychological risk factors (depression, anxiety, catastrophizing) for CPSP in the 4 weeks prior to surgery. Specifically, a mixed model analysis will be fit to the data using the Proc Mixed procedure in SAS.[56,57] Residual modeling will be performed to check for significant violations in the distribution and constant variance assumptions and determine if variance stabilizing or normalizing transformations should be applied. Furthermore, sensitivity analyses will be run considering dichotomous versions of the outcome variables using multiple logistic regression.

For the third study objective, we will describe the effects of the CBT intervention on 72hr post-operative pain severity, and 3- and 6-month rates of CPSP in comparison to patients who received treatment-as-usual. A mixed effects model will be fit with Treatment Group (intervention and usual care) as a between subject factor and Time (72hr, month 3 and 6) as a categorical within-subjects factor. We will include as baseline covariates any factors that differ significantly between the groups at baseline or show significant relationships with the outcome. Potential confounders (medical comorbidities, post-operative complications) will also be considered in the analysis.

The results from the mixed model analyses will be summarized by mean (SE) change from baseline for each group at each time point. The primary hypothesis will be evaluated at the alpha = 0.05 level and all contrasts/hypotheses will be considered exploratory and results will be interpreted with caution at alpha equal to 0.05 level. The primary goal will be to obtain reliable effect size estimates to inform larger studies. In that women are more likely to develop CPSP than men,[8,16] sex as a biological variable will considered as a possible moderator in all analyses.

RISK/BENEFIT ASSESSMENT:

1. Risks:

Opioid taper: As a part of the intervention and with the guidance of their trained coach, one-half of the subjects will be encouraged to gradually taper their opioid use in the month prior to surgery. It is possible that in doing so, subjects may experience the uncomfortable symptoms associated with opioid withdrawal. To avoid the emergence of these, subjects will be instructed to taper their dose gradually (no more than 10%/week), and will be provided with information on how to self-manage these symptoms should they arise. In addition, subjects will be instructed to contact their coach should the symptoms become severe, to receive guidance on how to temporarily cease and then restart taper attempts. In that subjects will have been regular users of opioids for at least three months prior to study enrollment, they will have developed a certain degree of physiologic tolerance, offering protection against any respiratory depressant effects during a taper pause.

Breach of Confidentiality: Participation in this study may constitute a social risk to the participant in that others may learn that he or she has chronic pain and is taking opioid medications. Due to the sensitive nature of this information, privacy and confidentiality will be strictly maintained in all aspects of participation. Consent and data collection sessions will take place in private rooms where strict privacy is enforced and all staff are HIPAA certified.

Acute Anxiety or Depressive Symptoms: It is possible that the opioid taper for the intervention group, or the upcoming surgery for both groups may precipitate unanticipated symptoms of acute anxiety or depression. As described below, co-PI Cheatle is a licensed clinical psychologist with over 40 years' experience in treating patients with chronic pain, will be available to assess and intervene with patients who experience these distressing symptoms during the pre-operative period.

2. Benefits:

The potential benefit for both the participants and broader segments of society is to improve pain outcomes following a very common procedure, TKA, ideally decreasing the severity of post-operative pain experienced and

the development of CPSP. Development of an effective intervention to address the risk factors for poor pain outcomes following TKA can guide clinical practice based upon evidence.

Participants will be informed that, other than any effect of the intervention for the treatment group, no direct benefit is expected to accrue to them from participation in the study.

3. Subject Privacy:
Consent and data collection sessions will take place in private rooms where strict privacy is enforced and all staff are HIPAA certified.

4. Subject Confidentiality:
All records will be kept strictly confidential. No one except the researchers will know the subjects are in a research study. Data forms for the collection of health and study data will be coded with each subject's unique identification number. No data form will identify the participants by name. Hardcopies of data forms will be kept in locked files with keys held only by the study investigators. All electronic data will be stored with the password and firewall protected REDCap data collection and management system of the U Penn School of Nursing. No presentation or publication of the results of this study will refer to the individual participants or present information that would identify any participant. All persons working on the proposed work will have completed HIPAA training and the Collaborative Institutional Training Initiative (CITI) Basic Courses in the Protection of Human Research Subjects and Biomedical Focus Responsible Conduct of Research (RCR) modules.

How will confidentiality of data be maintained? Check all that apply.

XX Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.

XX Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.

XX Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

XX Whenever feasible, identifiers will be removed from study-related information.

☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

☐ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

☐ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

☐ Other (specify):

5. Protected Health Information
Five types of protected health information will be collected, subject's name, telephone number, email address, medical record number, and date of birth. The first three are required to allow for the 3- and 6-month follow up, and the medical record number will enable us to extract data on post-operative pain and opioid use. Date of birth will be collected to verify age. These data will not be shared with persons not involved in the study, all of whom have completed HIPAA training.

6. Compensation:
Subjects will receive no compensation for participating in the study.

7. Data and Safety Monitoring:
The Penn Center for Substance Abuse Treatment (CSA) has a standing data and safety monitoring board (DSMB) which will be used for this study. The purpose of the DSMB and consistent with NIH guidelines is to

assure that the safety of subjects is protected while scientific goals are being met. Specifically, the CSA DSMB is charged with monitoring the safety of participants and the quality of data, as well as the appropriate termination of studies when significant benefits or risks have been uncovered or when it appears that a clinical trial cannot be concluded successfully.

All board members meet NIH requirements regarding background and experience, and none will have ethical conflicts including financial interest related to study outcome. Individuals invited to serve on the board disclose any potential conflicts in writing. The board meets every six months (unless more frequent meetings are deemed necessary) and is chaired by James McKay Ph.D. a faculty member within the Department of Psychiatry at the University of Pennsylvania. Other members of the board include Kevin Lynch, Ph.D. (senior statistician), David Metzger, Ph.D., Deborah Dunbar, MSN, CRNP who are faculty members or staff of the Perelman School of Medicine at Penn. Issues related to recruitment, safety and efficacy, whether the study questions are being answered, conflict of interest, confidentiality, and ongoing study review (including AEs, SAEs, and regulatory issues) are assessed.

Following each DSMB meeting, the designated member standing in for the Chair will make recommendations to Drs. Cheatle and Compton and a final report (edited by all Board members not in conflict with this project) will be prepared and submitted to NINR, the Penn IRB, and the FDA (if required) according to each body's reporting requirements. In addition, a Data Safety Monitoring Board report is issued to the NINR Project Officer with the annual progress report.

The DSMB will meet to review safety data every six months (unless more frequent meetings are deemed necessary). At least two weeks prior to each meeting, the investigative team will submit to the DSMB a DSMB Report detailing screening activities; reasons for screening failures; subject enrollment (actual vs. expected); sociodemographic characteristics of enrolled subjects; and subject disposition (including reasons for attrition). In addition, the number and nature (severity and relatedness to study procedures) of all adverse events will described. Finally, a random or purposive sample (depending on DSMB request) of subject case report forms (CRFs) will be submitted with the DSMB Report, to enable assessment of compliance with IRB requirements, conformance with informed consent requirements, verification of source documents and investigator compliance.

In the event that a subject scores high on the depression scale, a licensed clinical psychologist (co-PI Cheatle) will be available to assess immediately any patient who exhibits extreme anxiety, depression or suicidal ideation on routine screening or during the preoperative period. All research and clinical staff will call his cell phone when a patient with significant anxiety, depression or suicidal ideation is encountered. All patients who acknowledge extreme anxiety, depression or suicidal ideation and intent will be contacted immediately by Dr. Cheatle and an appropriate treatment plan will be enacted.

8. Investigator's Risk/Benefit Assessment:
Based on the characteristics of the risks associated with study participation, and efforts in place to minimize these risks, the risks to subjects are considered reasonable in relation to the anticipated benefits to research participants and others.

INFORMED CONSENT:

1. Consent Process:
Informed consent will be obtained from patients who express interest participating in the study by the trained study coordinator who has experience in obtaining consent from research subjects. It will be obtained in a private office at time that is convenient for the prospective subject. Specifically, the study coordinator will read out loud in English the consent form to the patient, stopping at regular intervals to assess the patient's level of understanding of the information in the consent form, clarifying content, and answering questions. Patients will be told that they need not sign the consent at this time, and that they may take it home to review for as long as they would like prior to deciding to provide informed consent. Patients will be assured that if they choose not to participate, it will have no effect on the medical care they receive or any other social retributions. Any evidence of mental impairment will be evaluated by the study coordinator via informal assessment; if impairment is suspected, the consent process will be halted, and either co-PI Compton or Cheatle will be called upon to further evaluate.

2. Waiver of Informed Consent:

Not applicable.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION:

The percent effort and qualifications of the members of the investigative team are more than adequate to conduct the research. Specifically, co-principal investigator, Martin Cheatle, PhD Cheatle will contribute 1.44 calendar months effort for the duration of the project and take primary responsibility for the development and pilot testing of the cognitive behavioral therapy (CBT) intervention, working closely with consultants Keefe and Rini. He will be responsible for training and monitoring the study coordinator/coach to effectively deliver the opioid tapering motivational interviewing (MI) component of the intervention and monitoring the fidelity of this delivery. He will serve as the CBT expert during the efficacy testing of the intervention and troubleshoot any issues that arise as participants undergo the 4-week training. In addition, he will take the lead in directing and interpreting the CBT feasibility and efficacy data in data analysis and dissemination activities and play a primary role in writing reports of the findings and subsequent grant applications.

Co-principal investigator, Peggy Compton, RN, PhD, will contribute 1.44 calendar months effort to the project over the two-year project duration. She will be responsible for obtaining IRB approval, directing development of the REDCap database, and overall coordination of the efficacy testing of the intervention. Working closely with Co-I Elkassabany, she will monitor subject recruitment and enrollment efforts and verify subject eligibility. She will also oversee the day-to-day activities and performance of the Study Coordinator, and be responsible for monitoring the accuracy, quality and completeness of data collection, ensure protocol fidelity, and compliance with all regulatory and funding agencies. She will direct data analysis, and play a primary role in dissemination of findings and grant writing.

The Co-investigator, Nabil Elkassabany, MD will contribute 0.6 calendar months during both years of the project. He will be responsible for working closely with Study Surgeons Lee and Nelson to identify and recruit potentially eligible patients for study enrollment. He will work with the Study Coordinator to establish eligibility and obtain informed consent. Importantly, he will serve as the primary liaison to the orthopedic surgeons and the surgery service to ensure effective collaboration as a means to achieve study objectives. In addition, he will assist with data interpretation and the dissemination of findings. Dr. Elkassabany will serve the primary study clinician, managing any health-related issues experienced by study subjects during study participation.

Statistician, Jesse Chittams, PhD, will contribute .45 calendar months effort to the project during Year 2 only. He will serve as the study statistician, working with the REDCap derived database to the complete the analysis as outlined in the Research Plan. Specifically, he will oversee data cleaning and variable construction, run interim analysis, and complete the descriptive and multivariate analysis required to meet the study specific aims. As results become available, he will work closely with the Co-PIs to refine the analytical plan as needed and contribute to the writing of dissemination materials.

The Study Coordinator/Coach, TBH, will devote 12 calendar months effort to the study over both years of the project. This individual will come to the project with experience in coordinating human subject clinical research studies and be responsible for enrolling subjects, scheduling study visits, all aspects of data collection, entering study data into REDCap, and engaging in ongoing communication with IRB, study setting and U Penn School of Medicine and Nursing, Department of Anesthesiology and Department of Orthopaedic Surgery. In addition, this individual will receive directed training and monitoring from Co-PI Cheatle to oversee delivery of the CBT and opioid tapering MI intervention. In this role, this individual will serve as a “coach” to the subjects, contacting them on a weekly basis prior to surgery, educating and motivating them to engage in preoperative opioid reduction.

Participants will be recruited from the nationally renowned Department of Orthopaedic Surgery at PPMC. Center surgeons perform approximately 1800 major TKAs per year, an estimated 20-30% of whom have been taking opioids for at least 3 months for the treatment of a chronic nonmalignant pain condition, resulting in a recruitment pool of 30 to 45 patients per month, providing an adequate source of the necessary 12-13 enrollments per month.

In addition, the facilities and resources are adequate to safely conduct the study. Situated within the Department of Psychiatry is the Center for Studies on Addiction (CSA), where Co-Principal Investigator Cheatle holds an appointment. A primary mission of the CSA is to continue to advance the cutting edge of knowledge on the nature of addiction and the best ways to treat this disorder. The CSA has, for the past 40 years, been an important

national and international resource for addictions research. The PI (Cheatle) has conducted large-scale studies on pain and opioid use disorders and suicide and has an established relationship at the primary recruitment site.

The CSA is housed in 16,400 sq. ft. of space in a building near the UPenn campus located adjacent to the primary recruitment site, PPMC. Dr. Cheatle has a locked private office space (5th floor, 3535 Market St., approximately 400 square feet). All faculty offices come equipped with locked filing cabinets, bookshelves, desk, minimum 4 GHz computer with HP printer, Windows XP service pack 3 operating system, Microsoft Office Professional (Word, Excel, PowerPoint, Access), SPSS or SAS statistical analysis software, and e-mail and internet access. Copier, printer, fax and scanner facilities are available in the center. In addition, the CSA has several meeting rooms with teleconferencing capabilities,

Co-Principal Investigator Compton and Biostatistician Chittams benefit from the extensive research resources at the University of Pennsylvania School of Nursing, which boasts the highest rate of NIH funding across nursing schools in the country. The School of Nursing has outstanding facilities and resources to accomplish its mission of excellence in research. Specifically, the *Office of Nursing Research (ONR)* support faculty and students in applying for, obtaining, and managing funding for scientific research projects. The ONR delivers a suite of services throughout the lifespan of a research grant - from conception to closeout. The ONR also provides highly-skilled statistical support, hosts an expertly staffed state-of-the-art nursing research laboratory, conducts mock reviews, offers guidance with IRB protocol submission and regulatory compliance, and provides editing services for scientific and English content of proposals. The ONR also provides various learning opportunities for faculty, staff and students through weekly colloquia and six face-to-face Responsible Conduct of Research seminars a year. Colloquia are presented by Penn Nursing faculty and guest lecturers from complementary disciplines to foster multidisciplinary research collaborations and initiatives.

For implementation of the proposed project, School of Nursing facilities include adequate computer, statistical support, and office resources necessary to undertake and complete the proposed research project successfully. Specifically, a wide range of computing resources is available at the University of Pennsylvania. Support for these resources is divided among a number of organizations. The broadest organization is led by the Vice Provost for Information Systems and Computing (ISC), which supports PennNet, the campus-wide network, providing both intra-campus communication, and access to the Internet. ISC manages the Data Warehouse, the University's central repository for administrative data, and oversees the development and maintenance of most of the administrative systems at Penn. Administrative systems are those used by all centers and the 12 schools in support of academic, business/financial, and research administration. ISC also provides a number of other campus-wide services, including development of technology training programs, evaluation of universally-used software (e.g., email, anti-virus packages, communications software), and management of software site licenses. ISC provides leadership on a number of technology issues, such as security and privacy.

Computing support is also available from the Office of Technology and Information Systems (OTIS) unit in the School of Nursing. OTIS supports a school-wide local area network, provides desktop support, offers routine training services, maintains liaison with technology representatives in each department, and runs two computer laboratories. The larger of these laboratories, containing 21 personal computers, is available to all members of the School of Nursing. The second laboratory, the Doctoral Computer Laboratory, is exclusively for the use of pre- and post-doctoral trainees. This lab is equipped with 8 personal computers with software resources including SAS, SPSS, STATA, ATLAS.

OTIS provides access for researchers to REDCap and to store data on a secure research server, which is backed up nightly, with weekly backups stored off site. The server is behind a firewall and is registered as a "Critical Host" by the University. This means OTIS follows all University polices regarding critical hosts: firewalls, access controls, timely patch management and anti-viral scans and software updates, and an enterprise system monitoring solution (allowing us to detect and address intrusion attempts). In the future, we will be enhancing the research server with the following: folder-based intrusion detection, encryption, and an off-site mirroring solution.

With respect to statistical support, the Office of Nursing Research (ONR) provides a team of highly skilled doctoral and master's level statisticians through the BECCA (Biostatistics * Evaluation * Collaboration * Consultation * Analysis) Lab, along with Penn Nursing research assistants and biostatistics graduate interns, who work with investigators to design, implement, analyze, and disseminate their research. Collaboration with a fully-supported, skilled statistician typically yields clearly articulated results that meet grant reviewers' expectations and peer-review. Statistical collaboration provides support in the areas of sample size, power analysis computation, data

management, statistical analysis, and results presentation. Expert at identifying and addressing potential issues, BECCA statisticians may suggest exploring alternatives such as more appropriate statistical designs, or perhaps modern modeling techniques. BECCA statisticians not only ensure statistical rigor and appropriateness, but also make sure that a study design is practical, feasible, and scientifically justifiable. The BECCA Lab is directed by and houses study biostatistician, Jesse Chittams.

Because the PAINTrainer intervention is web-based, and can be accessed from a computer, tablet or smartphone, dedicated university computer resources are not necessary for the proposed work; written into the budget is the purchase of four(4) ipads with internet connectivity to provide subjects who do not have a suitable device.

The School of Nursing is housed in Claire M. Fagin Hall, which was constructed in 1972 by funds from the Nurse Training Facilities Construction Grant Program of the Public Health Services, Department of Health and funds from the City of Philadelphia as a facility for three hospital programs. The co-PI applicant has her own locking office space (Claire Fagin Hall 204, approximately 170 square feet). All faculty offices come equipped with locked filing cabinets, bookshelves, desk, minimum 4 GHz computer with HP printer, Windows XP service pack 3 operating system, Microsoft Office Professional (Word, Excel, PowerPoint, Access), SPSS or SAS statistical analysis software, and e-mail and internet access. With the same resources, an adjacent cubicle space is dedicated to the study research assistant. Copier, printer, fax and scanner facilities are available on each floor.

Co-Investigator Elkassabany holds an appointment in the Department of Anesthesiology and Critical Care at Penn Medicine. The Department was founded over 50 years ago, and is enriched in a deep history of clinical care beginning with the first Department Chairman, Robert Dunning Dripps, who started the residency program at UPenn in 1943. UPenn Department of Anesthesiology provides anesthesia care to those having surgery, receiving trauma treatment, giving birth or undergoing major diagnostic procedures, offering comprehensive anesthesia care programs at HUP and PPMC (the proposed study site). The faculty include pain management specialists who provide interdisciplinary treatment of chronic pain. The Department boasts the *Penn Center for Anesthesia Research*, which emphasizes translational and interdisciplinary science, both within the department and other departments and institutes in the schools of medicine, nursing, arts and sciences, engineering and veterinary medicine, on Penn's unified campus. The resources listed below are fully available to Dr. Elkassabany and the research team to conduct of the study proposed herein. These resources, and the UPenn Anesthesia environment in general are considered state-of-the-art, in compliance with all Federal and State regulations, and will facilitate the timely completion of these studies.

Dr. Elkassabany has private locking office in the Perelman School of Medicine and shared office space in the primary recruitment site, PPMC. At both facilities, his office space is equipped with locked filing cabinets, bookshelves, desk, minimum 4 GHz computer with HP printer, Windows XP service pack 3 operating system, Microsoft Office Professional (Word, Excel, PowerPoint, Access), SPSS or SAS statistical analysis software, and e-mail and internet access. He enjoys full access to the centralized Department of Orthopaedic Surgery database through which patient randomization and data collection will be done.

Study Surgeons Lee and Nelson practice in the Department of Orthopaedics (Penn Orthopaedics) which boast a talented and specialized interdisciplinary team of health care providers dedicates to a whole-body approach to diagnosing and treating joint pain. They complete thousands of joint procedures a year (approximately 1100 primary TKAs and 500 TKA revisions), and provide services in sports medicine, cartilage repair, neuro-orthopedics, orthopaedic oncology, and trauma and fracture repair.

The Department of Orthopaedics provides the latest diagnostic techniques and the most advanced surgical and non-surgical options for a range of disorders, injuries and pain found in joints, muscles or bones. Penn Orthopaedics has 49 exam rooms, 4 Operating Rooms for Outpatient Procedures and 2 floors of Physical and Occupational Therapy at Penn Medicine University City. It brings together Penn clinicians from numerous specialties, including orthopaedics, rheumatology, physical medicine and rehabilitation, pain medicine and musculoskeletal radiology. This team-based model of care creates a seamless, integrated patient experience and the most efficient process towards an accurate diagnosis and appropriate treatment plan. Drs. Lee and Nelson each have their own 100 square feet offices with computers, printers, internet access and standard furniture.

In addition to clinical space, to support research activities, the Department of Orthopaedic Surgery provides space and resources for Clinical Research staff (up to 10 full time coordinators) associated with these studies. The

space is located in the department where we have 600 square feet of dedicated space, eleven PCs and eleven desks as well as storage for research binders and other confidential information. Electronic research files are stored on UPenn Health System secured servers behind the UPenn Health System firewall and are additionally protected through the use of limited access folders on the servers. Clinical data is maintained in PennChart which is a Penn-specific image of EPIC Electronic Medical Records Software (Epic Systems Corporation, Madison, Wisconsin).

The project is designed, staffed and budgeted to be successfully completed in 24 months. In consultation with Drs. Keefe and Rini, Dr. Cheatle will train the study coordinator coach on delivering the opioid taper MI intervention during months 1-3, during which time study start-up activities will take place. Enrollment will begin month 3; at a rate of 12-13 enrollments per month, we anticipate having enrolled 166 subjects (n=150, assuming 10% attrition) by study month 15, providing adequate time for 3- and 6-month follow up, and dissemination activities.

REFERENCES

1. http://aaos-annualmeeting-presskit.org/2018/research-news/sloan_tjr/
2. https://www.ncbi.nlm.nih.gov/pubmed/17403800
3. Inacio MCS, Paxton EW, Graves SE, Namba RS, Nemes S. Projected increase in total knee arthroplasty in the United States - an alternative projection model.O steoarthritis Cartilage. 2017 Nov;25(11):1797-1803. doi: 10.1016/j.joca.2017.07.022. Epub 2017 Aug 8.
4. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. J Bone Joint Surg Am. 2018 Sep 5;100(17):1455-1460. doi: 10.2106/JBJS.17.01617.
5. Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth. 2015 Apr;114(4):551-61. doi: 10.1093/bja/aeu441. Epub 2014 Dec 26.
6. Petersen, K.K., Simonsen, O., Laursen, M.B., Nielsen, T.A., Rasmussen, S. & Arendt-Nielsen, L. (2015). Chronic postoperative pain after primary and revision total knee arthroplasty.The Clinical Journal of Pain 31(1), 1-6. doi: 10.1097/AJP.0000000000000146
7. Petersen, K.K., Graven-Nielsen, T., Simonsen, O., Laursen, M.B., & Arendt-Nielsen, L. (2016). Postoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. Pain 157(7), 1400-1406. doi: 10.1097/j.pain.0000000000000531
8. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017 Oct 31;2(6):e627. doi: 10.1097/PR9.0000000000000627.
9. Lavand'homme P. (2017). Transition from acute to chronic pain after surgery. Pain 158(4), S50-S54.
10. Richebe P, Capdevila X, Rivat C. (2018). Persistent Postsurgical pain: Pathophysiology and preventive pharmacologic considerations. Anesthesiology 129: 590-607.
11. Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, Clauw DJ, Brummett CM. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain. 2016 Jun;157(6):1259-65. doi: 10.1097/j.pain.0000000000000516
12. Westermann RW, Anthony CA, Bedard N, Glass N, Bollier M, Hettrich CM, Wolf BR. (2017). Opioid consumption after rotator cuff repair. Arthroscopy 33(8): 1467-1472.
13. Parsons B, Schaefer C, Mann R, Sadosky A, Daniel S, Nalamachu S, Stacey BR, Nieshoff EC, Tuchman M, Anschel A. Economic and humanistic burden of post-trauma and post-surgical neuropathic pain among adults in the United States. J Pain Res. 2013 Jun 17;6:459-69. doi: 10.2147/JPR.S44939.
14. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009 May;9(5):723-44. doi: 10.1586/ern.09.20.
15. Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. Pain. 2018 Dec;159(12):2421-2436. doi: 10.1097/j.pain.0000000000001401.
16. Althaus A, Hinrichs-Rocker A, Chapman R, Arránz Becker O, Lefering R, Simanski C, Weber F, Moser KH, Joppich R, Trojan S, Gutzeit N, Neugebauer E. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain. 2012 Jul;16(6):901-10. doi: 10.1002/j.1532-2149.2011.00090
17. Buvanendran A, Della Valle CJ, Kroin JS, Shah M, Moric M, Tuman KJ, McCarthy RJ. Acute postoperative pain is an independent predictor of chronic postsurgical pain following total knee arthroplasty at 6 months: A

prospective cohort study. Regional Anesthesia and Pain Medicine. 2019; 44:e100036. http://dx.doi.org/10.1136/rapm-2018-100036.
18. Eisenach JC, Brennan TJ. Pain after surgery. Pain. 2018 Jun;159(6):1010-1011. doi: 10.1097/j.pain.0000000000001223.
19. Raja SN, Jensen TS. (2010). Predicting post-operative pain based on pre-operative pain perception: Are we doing better than the weatherman? Anesthesiology 112: 1311-1312.
20. McDonald S, Page MJ, Beringer K, Wasiak J, Sprowson A. Preoperative education for hip or knee replacement. Cochrane Database Syst Rev. 2014 May 13;(5):CD003526. doi: 10.1002/14651858.CD003526.pub3.
21. Riddle DL, Keefe FJ, Ang DC, Slover J, Jensen MP, Bair MJ, Kroenke K, Perera RA, Reed SD, McKee D, Dumenci L. Pain Coping Skills Training for Patients Who Catastrophize About Pain Prior to Knee Arthroplasty: A Multisite Randomized Clinical Trial. J Bone Joint Surg Am. 2019 Feb 6;101(3):218-227. doi: 10.2106/JBJS.18.00621.
22. Gibson E, Sabo MT. Can pain catastrophizing be changed in surgical patients? A scoping review. Can J Surg. 2018 Oct 1;61(5):311-318. doi: 10.1503/cjs.015417.
23. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD. IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain. 2019 Jan;160(1):45-52. doi: 10.1097/j.pain.0000000000001413.
24. Borsook D, Kussman BD, George E, Becerra LR, Burke DW. Surgically-induced neuropathic pain (SNPP): Understanding the perioperative process. Ann Surg. 2013; 257(3):403.412
25. Suzan E, Pud D, Eisenberg E. A crucial administration timing separates between beneficial and counterproductive effects of opioids on postoperative pain. Pain. 2018 Aug;159(8):1438-1440. ;
26. McAnally H. Rationale for and approach to preoperative opioid weaning: A preoperative optimization protocol. Preoperative Med. 2017; 6(19). Doi:10.1186/13741-017-0079-y.
27. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019 Apr 13;393(10180):1537-1546. doi: 10.1016/S0140-6736(19)30352-6.
28. Weber L, Yeomans DC, Tzabazis A. Opioid-induced hyperalgesia in clinical anesthesia practice: what has remained from theoretical concepts and experimental studies? Curr Opin Anaesthesiol. 2017 Aug;30(4):458-465. doi: 10.1097/ACO.0000000000000485.
29. Beck JS. Cognitive behavior therapy: Basics and beyond (2nd ed.). (2011) New York, NY: The Guilford Press.
30. Turk DC, Flor H. Etiological theories and treatments for chronic back pain. II. Psychological models and interventions. Pain, 1984. 19(3): p. 209-33.
31. Knoerl R, Lavoie Smith EM, Weisberg J. Chronic Pain and Cognitive Behavioral Therapy: An Integrative Review. West J Nurs Res. 2016 May;38(5):596-628. doi: 10.1177/0193945915615869. Epub 2015 Nov 24.
32. Baez S, Hoch MC, Hoch JM. Evaluation of Cognitive Behavioral Interventions and Psychoeducation Implemented by Rehabilitation Specialists to Treat Fear-Avoidance Beliefs in Patients with Low Back Pain: A Systematic Review. Arch Phys Med Rehabil. 2018 Nov;99(11):2287-2298. doi: 10.1016/j.apmr.2017.11.003. Epub 2017 Dec 14.
33. Monticone M, Ambrosini E, Cedraschi C, Rocca B, Fiorentini R, Restelli M, Gianola S, Ferrante S, Zanoli G, Moja L. Cognitive-behavioral Treatment for Subacute and Chronic Neck Pain: A Cochrane Review. Spine (Phila Pa 1976). 2015 Oct 1;40(19):1495-504. doi: 10.1097/BRS.0000000000001052.
34. Vugts MAP, Joosen MCW, van der Geer JE, Zedlitz AMEE, Vrijhoef HJM. The effectiveness of various computer-based interventions for patients with chronic pain or functional somatic syndromes: A systematic review and meta-analysis. PLoS One. 2018 May 16;13(5):e0196467. doi: 10.1371/journal.pone.0196467. eCollection 2018.
35. Ehde DM, Dillworth TM, Turner JA. Cognitive-behavioral therapy for individuals with chronic pain: efficacy, innovations, and directions for research. Am Psychol. 2014 Feb-Mar;69(2):153-66. doi: 10.1037/a0035747.
36. Rini, C., et al., Automated Internet-based pain coping skills training to manage osteoarthritis pain: a randomized controlled trial. Pain, 2015. 156(5): p. 837-48.
37. Bennell KL, Nelligan R, Dobson F, Rini C, Keefe F, Kasza J, French S, Bryant C, Dalwood A, Abbott JH, Hinman RS. Effectiveness of an Internet-Delivered Exercise and Pain-Coping Skills Training Intervention for Persons With Chronic Knee Pain: A Randomized Trial. Ann Intern Med. 2017 Apr 4;166(7):453-462. doi: 10.7326/M16-1714. Epub 2017 Feb 21.
38. Bennell KL, Nelligan RK, Rini C, Keefe FJ, Kasza J, French S, Forbes A, Dobson F, Abbott JH, Dalwood A, Harris A, Vicenzino B, Hodges PW, Hinman RS. Effects of internet-based pain coping skills training before

home exercise for individuals with hip osteoarthritis (HOPE trial): a randomised controlled trial. Pain. 2018 Sep;159(9):1833-1842. doi: 10.1097/j.pain.0000000000001281.
39. Cassin SE, Sockalingam S, Du C, Wnuk S, Hawa R, Parikh SV. A pilot randomized controlled trial of telephone-based cognitive behavioural therapy for preoperative bariatric surgery patients. Behav Res Ther. 2016 May;80:17-22. doi: 10.1016/j.brat.2016.03.001. Epub 2016 Mar 10.
40. Gade H, Friborg O, Rosenvinge JH, Småstuen MC, Hjelmesæth J. The Impact of a Preoperative Cognitive Behavioural Therapy (CBT) on Dysfunctional Eating Behaviours, Affective Symptoms and Body Weight 1 Year after Bariatric Surgery: A Randomised Controlled Trial. Obes Surg. 2015 Nov;25(11):2112-9. doi: 10.1007/s11695-015-1673-z
41. Lotzke H, Brisby H, Gutke A, Hägg O, Jakobsson M, Smeets R, Lundberg M. A Person-Centered Prehabilitation Program Based on Cognitive-Behavioral Physical Therapy for Patients Scheduled for Lumbar Fusion Surgery - A Randomized Controlled Trial. Phys Ther. 2019 Feb 21. pii: pzz020. doi: 10.1093/ptj/pzz020.
42. Wang L, Lee M, Zhang Z, Moodie J, Cheng D, Martin J. Does preoperative rehabilitation for patients planning to undergo joint replacement surgery improve outcomes? A systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2016 Feb 2;6(2):e009857. doi: 10.1136/bmjopen-2015-009857. Review.
43. das Nair R, Mhizha-Murira JR, Anderson P, Carpenter H, Clarke S, Groves S, Leighton P, Scammell BE, Topcu G, Walsh DA, Lincoln NB. Home-based pre-surgical psychological intervention for knee osteoarthritis (HAPPiKNEES): a feasibility randomized controlled trial. Clin Rehabil. 2018 Jun;32(6):777-789. doi: 10.1177/0269215518755426. Epub 2018 Feb 9.
44. Eccleston C, Fisher E, Thomas KH, Hearn L, Derry S, Stannard C, Knaggs R, Moore RA. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Database Syst Rev. 2017 Nov 13;11:CD010323. doi: 10.1002/14651858.CD010323.pub3.
45. Jung HJ, Yu ES, Kim JH.Combined Program of Cognitive-Behavioral Therapy for Insomnia and Medication Tapering in Cancer Patients: A Clinic-Based Pilot Study. Behav Sleep Med. 2019 Apr 9:1-10. doi: 10.1080/15402002.2019.1597718.
46. https://www.pbm.va.gov/AcademicDetailingService/Documents/Pain_Opioid_Taper_Tool_IB_10_939_P96820.pdf
47. Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, editors. Issues in Pain Measurement. New York: Raven Press; pp. 391-403, 1989 Advances in Pain Research and Therapy; Vol. 12.
48. Sullivan MJ, Bishop SR, Pivik J. The Pain Catastrophizing Scale: Development and Validation. Psychological Assessment 1995; 7(4): 524–532.
49. http://www.healthmeasures.net/explore-measurement-systems/promis
50. Littell RC, Milli GA, Stroup WW, Wolfinger RD. SAS System for Mixed Models, Cary, NC: SAS Institute Inc., 1996, pp. 633.
51. SAS Institute Inc. 2013. Base SAS® 9.4 Procedures Guide: Statistical Procedures, Second Edition. Cary, NC: SAS Institute Inc.
52. Little RJA. Modeling the drop-out mechanism in repeated-measures studies. Journal of the American Statistical Association. 1995;90:1112-21.
53. Allison PD. Missing Data. Sage University Papers Series on Quantitative Applications in the Social Sciences, 2001; 07-136. Thousand Oaks, CA: Sage.

Appendix

Chronic Post-Surgical Pain (CPSP) Checklist

If Brief Pain Inventory indicates that patient still has pain:	
1. Did the pain develop or increase in intensity after the surgical procedure?	○ YES ○ NO
2. Is the pain in the same location/area as the surgical procedure?	○ YES ○ NO
3. Is the pain distinct from other kinds of pain that were present prior to the surgery?	○ YES ○ NO ○ NA
4. Could your pain be described as burning, prickly, tingling, electric shocks and/or pins and needles?	○ YES ○ NO
5. Is the skin covering your painful area more sensitive to touch?	○ YES ○ NO