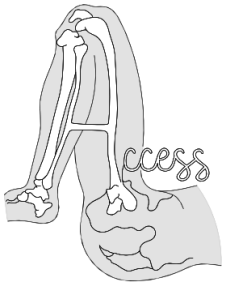

ACCESS

The Adductor Canal Catheter Effectiveness and Safety Study

KAISER PERMANENTE®

An Open-Label Randomized Noninferiority Clinical Trial of the Adductor Canal Catheter for Pain Control Post-Total Knee Arthroplasty

Conducted at:

Kaiser Permanente Northern California
San Leandro Medical Center
Division of Research

Sponsored by:

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0.0 SCHEMA

TITLE: Adductor Canal Catheter Effectiveness and Safety Study (ACCESS)

PRIMARY OBJECTIVE: Compare the effect of usual care with an adductor canal catheter (ACC) containing ropivacaine to the effect of usual care without an ACC on the second-postoperative-day pain levels among patients undergoing elective primary unilateral total knee arthroplasty (TKA)

SECONDARY OBJECTIVES: Among a sample of patients undergoing elective primary unilateral TKA who receive peri-articular anesthetic injections:

1) To compare the overall two-week levels of postoperative pain between those participants randomized to ACCs containing ropivacaine and those participants randomized to usual care without an ACC

2) To compare the use of opioid medications (in mean total morphine milligram equivalents) between those participants randomized to ACCs containing ropivacaine and those participants randomized to usual care without an ACC over the two-week postoperative period

3) To describe the incidence of complications related to ACC placement including infection, displacement, ACC-related clinic or emergency department (ED) visits

4) To conduct exploratory analyses to identify candidate predictors of differential response to the ACC

DESIGN: Randomized, open-label, two-arm, parallel-comparison noninferiority trial

POPULATION: Adults aged $\geq$18 years intending to undergo elective primary unilateral TKA at the KPNC San Leandro Medical Center

INTERVENTION: Participants will be randomized to one of two treatment arms:

- Adductor canal catheter placement in the pre-operative area immediately prior to TKA surgery

  OR

- No adductor canal catheter placement

DURATION: The intervention phase will occur between randomization and three days postoperatively (or until the ACC is removed by the participant or the ACC falls out spontaneously among ACC-randomized participants); the primary outcome will be measured on postoperative day 2, secondary pain and medication outcomes will be collected for two weeks postoperatively and the electronic medical record (EMR) will be examined for evidence of adverse events at 3 months postoperatively

SAMPLE SIZE: 132 participants randomized using balanced allocation to the two study arms

0.1 ACRONYMS USED IN THIS PROTOCOL

ACB = Adductor Canal Block
ACC = Adductor Canal Catheter
ACCESS = Adductor Canal Catheter Effectiveness and Safety Study
AE = Adverse Event
DOR = Division of Research
DSM = Data and Safety Monitor
ED = Emergency Department
EMR = Electronic Medical Record (KPNC HealthConnect)
ERAS = Enhanced Recovery After Surgery
ICH = International Council for Harmonization
IDE = Investigational Device Exemption
IND = Investigational New Drug
IRB = Institutional Review Board
KPNC = Kaiser Permanente, Northern California
MCID = Minimum Clinically Important Difference
NRS = Numerical Rating Scale
NSAID = Non-Steroidal Anti-Inflammatory Drug
PAI = Peri-Articular Injection
PHI = Protected Health Information
PROMIS = Patient-Reported Outcomes Measurement Information System
RCT = Randomized Clinical Trial
SAE = Serious Adverse Event
SLN = San Leandro (KPNC Medical Center)
TKA = Total Knee Arthroplasty
UP = Unanticipated Problem

1.0 INTRODUCTION

1.1 STUDY RATIONALE

Pain management for patients undergoing TKA is central to the successful recovery of patients from surgery. In the past, pain control has relied heavily on the use of opioid analgesics, which have resulted in serious medical and chemical-dependency problems. In an effort to reduce the use of postoperative opioid medications, multi-modal (non-opioid) analgesic techniques have emerged in recent years, including the use of peri-articular anesthetic injections. An additional technique in widespread use is the adductor canal catheter, a medical device that consists of a tunneled catheter connected to an analgesic solution-containing reservoir that slowly infuses the anesthetic over the first 2-3 postoperative days.

Despite its widespread use, the incremental benefit of the ACC beyond the other widely used analgesic methods is poorly understood. Since its use is associated with known risks (such as bleeding and patient anxiety if it falls out spontaneously) and high expense, objective data regarding the value of the ACC is urgently needed in order to make rational, evidence-based decisions about whether use of the ACC should be promoted or discouraged. To address this important evidence deficiency, The Permanente Medical Group is funding this clinical trial to better understand the proper role of the ACC in the optimal postoperative care of patients undergoing TKA.

1.2 BACKGROUND

TKA is a successful treatment option for end-stage arthritis of the knee. With an aging population and expanding indicated age-range, the annual volume of TKA surgery in the United States currently exceeds 600,000 cases and is projected to continue to increase over the next decade (1,2). Within Kaiser Permanente, we perform over 7,000 TKAs annually in Northern California alone. Published success rates following TKA surgery vary depending on the definition of success but patient satisfaction rates of at least 80% are typical (3). While causes of dissatisfaction following TKA surgery are varied, pain is the most common reported reason (4). Further, published data reported from our own institution has found that the most frequent cause of early inpatient readmission and ED visits after TKA surgery is pain (5). Pain is also one of the primary reasons patients are unable to be discharged home directly after surgery in our institution.

The last decade has seen several significant advances in the management of pain following TKA surgery. “Multi-modal anesthesia” protocols have been developed to utilize non-opioid therapies during the recovery period (6). Historically TKA patients were prescribed Patient-Controlled Analgesia machines to self-administer parenteral opioid-based pain medication. While their use enabled patients to take control of their pain medication administration, the negative impact of these parenteral opioids – including dizziness, nausea, vomiting and respiratory depression – on their recovery after surgery has been well-described (7,8).

Neuraxial and regional anesthetic techniques have been utilized in an effort to decrease reliance on opioid medications. While femoral nerve blocks were historically used in the management of post-op pain in lower extremity surgery, the block of the motor component of the femoral nerve resulted in reports of quadriceps weakness resulting in inability to work with therapy, delayed discharge to home and inadvertent falls (9,10). Adductor canal blocks (ACB) and catheters (ACC) have been described to provide a blockade to the entirely sensory saphenous nerve, as well as the vastus medialis nerve and the posterior branch of the obturator nerve without impacting the motor branches of the femoral nerve. These blocks offer an anterior and medial-based sensory blockade of the knee (11). The use of ACCs/ACBs has allowed for complete participation in post-operative rehabilitation with far fewer reports of quadriceps weakness (12). ACCs and ACBs have seen widespread adoption throughout Kaiser Permanente in the last 2 years with all but one facility in Northern California utilizing them.

In the case of an ACC, a dedicated anesthesia provider uses a portable ultrasound machine to position the catheter prior to surgery in the pre-op area or after surgery in the post-anesthesia care unit. Once the catheter is placed, it is attached to a pump and reservoir containing 450 cc of 0.2% ropivacaine solution which, when activated, releases the medication in a controlled fashion. The rate of administration can be adjusted by the patient. Currently these catheters are left in place for 3 days after surgery and are then removed by the patient at home. While the quadriceps weakness associated with

femoral nerve blocks and catheters is largely avoided in the use of adductor canal catheters, the use of ACCs is not without potential complications (13).

Another modality described for the management of post-op pain following TKA surgery has been the peri-articular injection (PAI) – an intra-operative injection into the peri-articular soft tissue of bupivacaine, epinephrine, clonidine and ketorolac (14). Its use in TKA surgery coincided with adoption of Enhanced Recovery After Surgery (ERAS) protocols in which early mobility and alternatives to opioid therapy are employed. The impact of both the PAI and ERAS protocols in TKA patients' outcomes have been well-described (15–17). PAI use in TKA surgery is now nearly universal within Kaiser Permanente and is considered one of the modalities which satisfies the ERAS metric of multi-modal pain management in elective TKA.

In 2016, CMS initiated the Comprehensive Care of Joint Replacement program to help reduce the costs associated with a total knee or hip replacement. This program shifted the reimbursement model for total hip and knee replacement surgery from one of fee-for-service to one of a single reimbursement for the entire episode of care. The introduction of this "bundled payment" reimbursement model has resulted in a renewed focus on all costs related to the total joint care pathway and has had a direct impact on the reduction of length of inpatient stay following total joint arthroplasty across the nation.

Inpatient hospital admission is one of the greatest contributors to the cost of the episode of care. In the last 7 years we have seen our length of stay for total knee replacement patients reduced from 3 days to less than one day. One of the major hurdles in safe patient discharge after TKA surgery is adequate pain control. The adoption of a multi-modal pain reduction strategy and, in particular, the use of the peri-articular injection has facilitated this reduction in LOS. Part of the rationale for the addition of adductor canal catheters to this pain-reduction strategy is to help improve post-operative pain and reduce LOS. In KPNC SLN, where we perform over 1,000 primary unilateral TKA surgeries each year, utilization of ACCs is variable among surgeons. Comparing length of stay in our primary TKA patients, we see the same rate of same day discharge among providers who use ACCs and those who do not. Further, a pilot study conducted at our facility in 2018 found only a very small (and clinically unimportant) difference in post-operative day 2 (when the effects of the PAI would be expected to have worn off) numerical pain score between patients with an ACC and those without. These findings are similar to a recently published randomized control study which found no difference in pain levels or opioid consumption between TKA patients with PAI alone or with PAI plus ACB (18). Our pilot study has also identified several complications associated with ACCs including leaking, dislodging, bleeding, hematoma development and prolonged neuropraxia, resulting in ED visits and phone calls to address these issues.

The entire cost of adductor canal catheters includes the pump, tubing and medication as well as the FTE provider who places them and the potential cost of ED visits or phone calls/office visits to address complications associated with the catheters. Given the cost of the catheters themselves ($400) and the number of primary TKA surgeries performed annually in KPNC alone (> 7,000), the annual cost to our organization is estimated to be more than $4 million.

Therefore, we propose this randomized, open-label, parallel-comparison noninferiority clinical trial to determine whether the effectiveness of these catheters justifies their cost.

1.3 STUDY DESIGN

This is a randomized, open-label, two-arm, parallel-comparison noninferiority clinical trial of usual care with an ACC placed preoperatively compared to usual care without an ACC among adult patients undergoing elective unilateral TKA at the KPNC San Leandro Medical Center (Figure).

All patients meeting eligibility criteria will be introduced to the study by the treating orthopedist and PI, Dr. Adrian Hinman, at the patient's first clinic visit. If the patient expresses interest in study participation, they will be consented over the phone by the clinic Physician's Assistant (PA). Baseline data will be obtained via a telephone call with the study Research Assistant 7-10 days prior to the date of surgery. Randomization will occur in the preoperative area immediately prior to surgery. Patients will keep a daily diary of their pain levels and analgesic medication use for two weeks postoperatively and will be called by the study Research Assistant on post-op day two and day 14. A single electronic

medical record (EMR) data extraction for adverse events (focusing on emergency department and inpatient visits) will be conducted at 30 days postoperatively.

The primary outcome is the absolute pain score on post-op day two, measured on an 11-point numerical rating scale; the noninferiority margin for this comparison is set *a priori* at 2.0 points. Secondary outcomes include the total amount of opioid consumed over the two-week post-op period, the overall pain scores over the two-week post-op period, and adverse events directly attributed to the ACC.

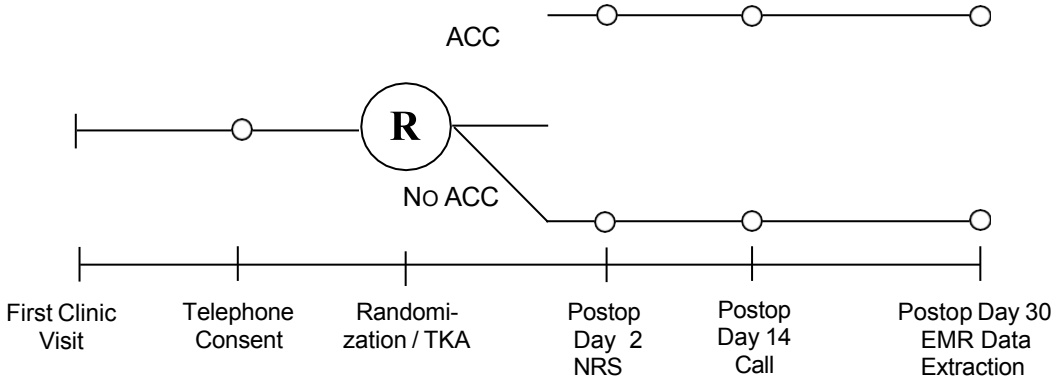


Figure: Study Design Schema

2.0 OBJECTIVES

2.1 PRIMARY OBJECTIVE

To compare the effect of usual care with an ACC containing ropivacaine to the effect of usual care in the absence of an ACC on the second-postoperative-day pain levels among patients undergoing elective primary unilateral TKA who receive peri-articular anesthetic injections

2.2 SECONDARY OBJECTIVES

Among a sample of patients undergoing elective primary unilateral TKA who receive peri-articular anesthetic injections:

1) To compare the overall two-week levels of postoperative pain between those participants randomized to ACCs containing ropivacaine and those participants randomized to usual care without an ACC

2) To compare the use of opioid medications (in mean total morphine milligram equivalents) between those participants randomized to ACCs containing ropivacaine and those participants randomized to usual care without an ACC over the two-week postoperative period

3) To estimate the incidence of complications related to ACC placement including infection, displacement, ACC-related outpatient clinic or ED visits

4) To conduct exploratory analyses to identify candidate predictors of differential response to the ACC; potential interacting variables for these analyses will include demographics, baseline pain NRS scores, clinical comorbidities and secondary outcome measures.

2.3 PROPOSED SUBGROUPS

No subgroup analyses are proposed for this trial. As noted above (2.2, Secondary Objective #4), we will conduct exploratory analyses of potential interacting variables associated with differential (positive) response to the use of the ACC. As exploratory investigations, it is acknowledged that these analyses will likely be underpowered and are hypothesis-generating only.

3.0 STUDY PARTICIPANTS

3.1 INCLUSION CRITERIA

All study participants will be active members of the KPNC health plan, since all recruitment activities and interventions will take place in KPNC medical facilities.

The inclusion criteria for the ACCESS study, and their rationales, are:

1. Age > 18 years	1. Age of consent
2. Intending to undergo elective primary unilateral TKA at the KPNC SLN Medical Center	2. Indication for use of the ACC; study site is KPNC SLN Medical Center
3. Patient ambulates independently	3. Non-ambulatory patients may have atypical postoperative recovery courses

3.2 EXCLUSION CRITERIA

The exclusion criteria for the ACCESS study, and their rationales, are:

1. Patient declines use of ACC	1. Patient not eligible for ACC study arm
2. Surgeon decides that an ACC will not be placed for any reason	2. Patient not eligible for ACC study arm
3. Known hypersensitivity to ropivacaine or any alternative anesthetic for ACC use	3. Patient not eligible for ACC study arm
4. Hypersensitivity or inability to tolerate peri-articular injections of clonidine, epinephrine, bupivacaine and ketorolac	4. Participants in both arms of the trial are required to undergo peri-articular anesthetic injections
5. Any evidence of substance-use disorder in past year	5. Opioid use is a secondary study outcome measure
6. Non-English speaking	6. Study instruments are all in English
7. Failure to complete all baseline study instruments prior to surgery	7. No baseline measurement available for calculating change
8. Requires secondary procedure at time of TKA (e.g., removal of hardware)	8. Complex surgery may cause change in outcome measures independent of study objectives
9. Not intending to use spinal anesthesia for TKA procedure	9. Atypical surgical approach
10. Actively enrolled in KPNC chronic-pain program	10. Opioid use is a secondary study outcome measure
11. Having been prescribed long-acting opioid (e.g., Oxycontin, MS Contin) within 90 days prior to enrollment	11. Pre-surgery major opioid use may complicate measurement of post-surgery opioid use
12. Inability to tolerate any oral NSAID or acetaminophen or any short-acting opioid	12. NSAIDs, acetaminophen, and short-acting opioids are used for analgesia for all participants

These exclusion criteria are established for safety and to ensure consistency in the participant sample.

3.3 RANDOMIZATION

Randomization will be balanced (i.e., using an allocation ratio of 1:1) and blocked (using randomly chosen block sizes of 2, 4, and 6); no stratified randomization will be used.

The randomization list will be generated by Dr. Catherine Lee (study Biostatistician) using the “ralloc.ado” procedure in Stata (this procedure creates a balanced, blocked, and self-documenting randomization list) (19). The randomization list will then be used by study staff to create a set of sequentially numbered, sealed opaque envelopes which contain cards on which the randomization

assignment for each study participant is noted (the cards will be covered in aluminum foil inside the envelopes to defeat "hot-lighting" the envelopes). A copy of the randomization list will be given to a DOR investigator who is not affiliated with the ACCESS study, as backup in case the randomization envelopes are misplaced or stolen, and as validation for any study audits.

The randomization envelopes will be stored in a locked box that will be stored in a locked cabinet in the pre-op area, accessible only to appropriate study personnel. As noted above, randomization will occur in the pre-operative area prior to the participant being transported to the operating room for their surgery.

3.4 REFUSAL/REJECT LOG

A log of potential participants who decline to enter the study or who are deemed ineligible by the application of entry inclusion and exclusion criteria will be kept in order to judge the representativeness of those who consent to be randomized, consistent with CONSORT guidelines (20). If the individual and the IRB permits, data collected in the refusal/reject log will include the individual's age, gender, race/ethnicity, NRS pain score, and reason for rejection or refusal.

3.5 RECRUITMENT

3.5.1 CLINICAL PERSONNEL AND SITE

Participants will initially be recruited from Dr. Hinman's TKA patient list at KPNC San Leandro. If recruitment lags behind *a priori* goals, it will be expanded to include the TKA patients of other San Leandro orthopedists (Drs. Kasey Cortese and David Lee have agreed to complete their research trainings and participate in patient recruitment should Dr. Hinman's patients be insufficient to maintain recruitment at the required levels). KPNC San Leandro will remain the only clinical site; no patients will be recruited from any other KPNC facility.

3.5.2 RECRUITMENT STRATEGY AND MECHANISM

Patients will first be notified of the existence of the study by Dr. Hinman (or another participating orthopedic surgeon) at their first clinic visit. After it has been determined that TKA is indicated and the patient is intending to undergo surgery, the orthopedist will briefly introduce the study to the patient. Unless the patient expresses clear disinterest in participating in the trial, they will be given an ACCESS clinic introductory packet by the clinic Patient Navigator along with their usual pre-operative preparation materials. This packet will contain the following items: informational materials about the ACCESS trial, two copies of the unsigned consent form, two copies of the unsigned HIPAA authorization form, one copy of the Research Subject's Bill of Rights, the baseline questionnaire, and a postage-paid reply envelope. An appointment will be made with the study Physician's Assistant for a telephone information-and-consent call with the patient.

3.6 PARTICIPANT COMPENSATION

Participants will be compensated $50 for completing all study procedures including all pre-randomization activities, proceeding through randomization, and completing their post-operative data collection including the pain/medication diary and study-related telephone calls. Payment will be made in the form of a gift card to a commercial retail store (typically Target, Safeway, or Amazon).

4.0 MEASUREMENTS

4.1 PRIMARY OUTCOME

The primary outcome measurement for this study is the Numerical Rating Scale for pain recorded on the second postoperative day. The pain NRS is a 0-to-10 ordinal scale (with anchors, 0 = "no pain" and 10 = "worst possible pain") which the participant selects in response to the prompt, "What number best describes your typical pain in the past 24 hours?". Several different variations of pain-intensity measures exist but there is good evidence that numerical rating scales are easy to administer

with high respondent acceptability, high reliability (21,22), excellent validity when compared to visual analogue scales (21) and widely recommended as a core measure in pain trials (23).

The primary outcome will be obtained by the study Research Assistant via a telephone call on the second postoperative day. If the Research Assistant is unable to reach the participant by phone, the pain NRS score for the second postoperative day on the daily diary will be used for this measurement, if the diary is returned to the DOR.

4.2 SECONDARY OUTCOMES

Originally, the secondary outcomes included the PROMIS Global Health-10 short form and the Knee injury and Osteoarthritis Outcome Score short form (KOOS Jr). However, after further reflection among the study investigators, it was decided that these measures of symptoms and functions provided little meaningful outcome data among a sample of patients soon after knee replacement. Therefore, these measures were discarded as secondary outcome measurements.

However, the investigators decided that consumption of opioid medication in the 15 days postoperatively (as provided in the postoperative pain-and-medication diary) provided an important and meaningful secondary outcome measure for assessing the analgesic effectiveness of the ACC. The main secondary outcome measure will be the total number of 5mg oxycodone tablets (provided to all patients on discharge) consumed over the 15-day postoperative period. This change is reflected in the study schema, above.

4.3 OTHER MEASUREMENTS

In addition to these instruments, we will also collect data on patient demographics, clinical history of knee pain (approximate length of time with symptoms, prior interventions, history of ipsilateral knee trauma, etc.), prior medication use, and relevant comorbidities (e.g., gout, inflammatory arthritis).

5.0 INTERVENTIONS

5.1.1 ACTIVE AND CONTROL CONDITIONS

Participants in the intervention arm will have implanted a bupivacaine-filled ACC immediately prior to surgery, according to usual preoperative-care practices (for the patients of those orthopedists who use the catheters). As a pragmatic trial, there will be no change in the nature of the device or the manner in which it is implanted and managed postoperatively. All other aspects of pre-surgical, operative, and post-operative care will be conducted as per usual clinical practice.

Participants in the control arm will receive identical clinical care with the exception that no ACC will be placed in their leg prior to surgery.

5.1 STUDY DEVICE

The adductor canal catheter is a device which is placed by a trained anesthesia provider in order to apply analgesia to the anterior portion of the knee. It consists of a catheter, tubing and an adjustable time-release pump and reservoir. The reservoir is filled with 450 ccs of 0.2% ropivacaine. The catheter is inserted into the adductor canal, which contains the purely sensory saphenous nerve - a branch of the femoral nerve which supplies the anterior portion of the knee. The pump releases the ropivacaine in a controlled release fashion over 48-72 hours depending on the adjustable rate of the pump. When the reservoir is empty, the catheter is removed by the patient and disposed.

5.1.3 SOURCE AND MANAGEMENT OF DEVICE

The ACC is an FDA-approved medical device in current use within KPNC. The device is considered a standard-of-care instrument and, therefore, does not require special handling for use in a research study. The ACCs used for this study will be stored in the usual hospital locations and be filled with the bupivacaine anesthetic by the hospital pharmacist, in the usual manner. The device will be placed in the legs of the intervention-allocated patients by a KPNC anesthesiologist according to usual clinical practice and it will be removed by the patient by postoperative day three, according to the manufacturer's instructions. The device will be discarded by the patient at home and not be returned for study purposes.

5.1.4 CONCOMITANT MEDICATIONS AND RESTRICTIONS

All patients will receive periarticular anesthetic injections at the time of surgery. Postoperatively, all patients will receive a standard set of oral analgesic medications for pain control. These medications include ibuprofen 600 mg orally every 8 hours, acetaminophen 1 gm orally every 8 hours and oxycodone 5 mg 1 tab orally every 6 hours as needed for moderate pain or 2 tabs orally every 6 hours as needed for severe pain not relieved by other analgesics (patients also receive aspirin 81 mg orally twice daily for venous thromboembolism prophylaxis). Use of analgesic medications in the two weeks after surgery will be reported by the patient through the use of the daily patient diary (for those patients who are not discharged to home on the same day of surgery, we will also obtain data on the analgesic medications given to the patient while in the hospital). As a pragmatic trial, patients are free to use any recommended postoperative services, such as physical therapy in mind-body techniques for pain management.

5.1.6 ADHERENCE MEASURES

Because placement of the ACC will be carried out immediately after randomization by the attending anesthesiologist (for those participants randomized to receive an ACC), there is little opportunity for intervention non-adherence. However, It is anticipated there may be an occasional patient who develops "cold feet" immediately after randomization and declines the randomized assignment); these patients are randomized and will be asked to follow through with all other study - related procedures, including data collection. As the primary analysis will be intention-to-treat, participants will be analyzed in the group to which they were originally randomized, regardless of their actual adherence to the intervention.

Most data collection will occur in the two postoperative weeks. Both the baseline and closeout questionnaires will be administered over the phone, to help ensure completeness of data collection. All participants will be asked to complete a daily pain and medication diary which they will return to the Division of Research, where their data will be entered into a REDCap database with full range and logic checking. All patients will be called two days after surgery (for collection of the primary pain NRS outcome measurement), one week after surgery to encourage adherence with data collection, and again 14 days after surgery for completion of the closeout questionnaire and a reminder to return the daily diary to the DOR. Regular reports of the completeness of data collection will be generated and reviewed by all study personnel on a regular basis to ensure high quality of data collection. Any evidence of problems in data collection or quality will be addressed quickly and monitored carefully.

6.0 STUDY PROCEDURES

6.1 INITIAL CONTACT

Patients' first introduction to the ACCESS study will occur during their first visit with their orthopedist during which the decision regarding proceeding to TKA will occur. Using an IRB-approved script, the orthopedist will briefly describe the rationale and essential details of the study. The patient will be encouraged to ask questions and, if the patient expresses interest in learning more about the study, the orthopedist will inform the Patient Navigator.

After the patient's visit with their orthopedist, the Patient Navigator will hand to the patient a packet containing: informational materials about the ACCESS trial, two copies of the unsigned consent form, two copies of the unsigned HIPAA authorization form, one copy of the Research Subject's Bill of Rights, the baseline questionnaire, and a postage-paid reply envelope. An appointment will be made with the study Physician's Assistant for a telephone information-and-consent call with the patient.

6.2 TELEPHONE SCREENING AND CONSENT CALL

At the appointed time, the study PA will call the patient at home and present the study details to the patient using an IRB-approved script and answer any questions the patient may have. If the patient expresses a desire to enroll in the study, the PA will ask the patient to retrieve the consent and HIPAA Authorization forms from the clinic study packet; the PA will then walk through all elements of the consent form with the patient, again using an IRB-approved telephone script. If, after this procedure, the patient is still interested in enrolling in the study, they will sign their copy of the consent form. The same procedure will then be repeated for the HIPAA authorization form. The PA will then ask the patient to put both sign forms in the postage-paid reply envelope and mail them back to the orthopedics department at the SLN Medical Center. The PA will document this call in the patient's medical record.

During this call and after the consent is obtained, the PA will also conduct an eligibility screen to ensure that the patient meets all inclusion and none of the exclusion criteria; these will be documented in the study screening form.

6.3 PREOP TELEPHONE CALL

Approximately one-week prior to the participants TKA surgery, the study Research Assistant will call the patient at home to ensure that they are still intending to follow through with all study procedures and to ensure they understand the details of their further participation, including the randomization immediately prior to surgery. If the patient has any questions, they will be referred to the DOR co-PI (Dr. Avins) for further discussions. If the patient expresses any reservations about their further involvement in the study, they will not be randomized. If the patient is fully intending to continue with the study, the RA will administer the baseline questionnaire over the phone before ending the call.

During this call, the RA will also conduct a repeat eligibility screen to ensure that the patient meets all inclusion and none of the exclusion criteria.

6.4 DAY OF SURGERY

On the day of surgery, all preoperative activities will proceed as usual for patients undergoing TKA at the SLN Medical Center. The orthopedic surgeon, when meeting with the patient prior to surgery, will confirm once more that the patient is intending to be randomized and participate in the study. Note that there will be no additional consent procedure (as advised by the regulatory specialist with the KPNC DOR Clinical Trials Unit).

At the time when an ACC would normally be placed by the anesthesiologist (if the patient was going to have an ACC placed), the orthopedist or study PA will obtain the next consecutive randomization envelope and open it, revealing to the patient and anesthesiologist the randomization assignment. If the participant is randomized to placement of the ACC, the anesthesiologist will proceed with ACC placement as usual. If the participant is randomized to non-placement of the ACC, no ACC will be inserted and the remaining preoperative activities will continue as usual.

After surgery (whether the participant will be discharged to home on the day of surgery or admitted to the hospital), the patient will be given a packet containing all instructions for further participation, their daily pain-and-medication diary, and the closeout questionnaire). They will be told to begin filling out their diary the following day.

6.5 2-DAY FOLLOW-UP TELEPHONE CALL

On the afternoon of the second postoperative day, the study Research Assistant will call the participant at home to obtain their numerical rating pain score for the primary study outcome. They will inquire of the patient if they have any questions regarding their further participation, ensure that the participant understands their research-related responsibilities, and encourage adherence with all data

collection. Note that this call is separate from any clinical telephone calls made to the participant from the orthopedics department.

6.6 1-WEEK FOLLOW-UP TELEPHONE CALL

One week following the date of surgery, the study Research Assistant will call the participant at home to ensure that they are continuing to fill out their daily participant diary, inquire about any potential adverse events, answer any questions, and remind the patient that there will be a closeout phone call in another week.

6.7 2-WEEK CLOSEOUT TELEPHONE CALL

Two weeks after the date of surgery, the study Research Assistant will call the participant at home and conduct the closeout interview. The RA will again inquire about any potential adverse events since the prior call (including follow-up of previously reported AEs), answer any questions, then conduct the closeout questionnaire interview. Towards the end of the call, the RA will then instruct the participant to place their daily diary into the postage-paid reply envelope and mail the envelope to the DOR as soon as possible.

6.8 24-WEEK DATA EXTRACTION

Approximately 24 weeks after surgery, the study programmer will extract relevant clinical information from Clarity, primarily for the purpose of assessment for evidence of SAE's between two and 24 weeks postoperatively. Any evidence of potential SAE's during this time will be investigated by the DOR co-PI and reported in accordance with regulatory requirements.

6.9 VISIT WINDOWS

The following lists the follow-up visit windows outside of which data collection will be considered a protocol deviation:

One-week preoperative telephone call: Ten days prior and four days following
2-day follow-up telephone call: No window
1-week follow-up telephone call: No data collection at this call
2-week closeout telephone call: Two days prior and three days following
24-week data extraction: Two months following the 24-week timepoint (data will be collected only for the period from surgery to 24 weeks postoperatively

7.0 ADVERSE EVENT REPORTING

7.1 CLASSIFICATION OF ADVERSE EVENTS

The ACCESS study uses the definitions of an adverse event (AE) and a serious adverse event (SAE) established by the International Conference on Harmonization (ICH) guidelines on Clinical Safety Data Management (32). These definitions are:

An adverse event (also known as “non-serious adverse event” **(NSAE)**) is any untoward medical occurrence in a patient or clinical investigation subject administered a study intervention and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an intervention, whether or not considered related to the intervention. Note that adverse changes in the outcome measures of the study (e.g., pain scores) are not considered adverse events and will not be reported as such. Symptoms or other abnormalities that were present prior to a participant's randomization will not be considered adverse events (i.e., these will be treated as pre-existing conditions and not-study related); similarly, therapies (e.g., surgery) to treat a pre-existing condition are not reportable adverse events. Note that clinically meaningful *worsening* of a pre-existing condition is considered an adverse event and will be reported as such.

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

1) results in death
2) is life-threatening

3) requires inpatient hospitalization or prolongation of existing hospitalization
4) results in persistent or significant disability/incapacity
5) is a congenital abnormality or birth defect
6) is an important medical event that may not result in death, be life-threatening or require inpatient hospitalization but if, based on appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent a serious adverse event.

An Unanticipated Problem (UP) is a subset of adverse events with special reporting requirements. The definition of a UP is:

1) It is unanticipated (in nature, severity, and/or frequency), and
2) It is at least possibly related to participation in research, and
3) It suggests greater risk of harm to participant(s) or others than previously known or recognized (includes participants, family members, and research staff).

7.2 REPORTING OF SERIOUS ADVERSE EVENTS

While the ACCESS study will not be conducted under an FDA IND or IDE, we will observe similar reporting requirements, modified for compatibility with the KPNC IRB guidelines. Deadlines for reporting are described below. The form for reporting will be the usual ACCESS SAE report form for early reportable SAE's and UP's and the relevant DSM report AE/SAE table (which will also be forwarded to the IRB following each DSM meeting)

Report to the IRB and DSM within 1 business day and at annual renewal

Unanticipated death at least possibly related to study (i.e., fatal UP)

Report to the IRB and DSM within 10 business days and at annual renewal

SAE's that are UP's

New safety information becomes available that is at the level of an UP

Report only at annual renewal (IRB) or at each DSM meeting

Death that is NOT a UP (i.e., all deaths that are not reported within 1 day)

7.3 REPORTING OF NON-SERIOUS ADVERSE EVENTS

All non-serious AE's will be recorded on the study AE form. All AE's will be reported in aggregate and individually to the IRB annually and to the DSM at each scheduled DSM conference call.

7.4 CRITERIA FOR TREATMENT DISCONTINUATION

Any ACC-allocated participant who exhibits a serious untoward reaction to the study ACC that, in the opinion of the investigators or the participant's treating physician, would render study continuation contrary to the best interest of the participant will be withdrawn from the study intervention. Any participant who is withdrawn from study intervention will be encouraged to continue all study-related data collection, in order to permit an intention-to-treat analysis with minimal data imputation.

7.5 CRITERIA FOR PARTICIPANT STUDY WITHDRAWAL

All participants will be encouraged to adhere to all study procedures even if they decline their randomized treatment assignment or prematurely remove the ACC, in order to permit an intention-to-treat analysis. If a participant expresses an intention to withdraw from the study prior to the two-week closeout time point, he/she will be questioned about the reasons for their intended withdrawal and attempts at resolving barriers to continued participation will be made (e.g., increasing contact with study investigators, shortening questionnaire time). Any participant may withdraw entirely from the study at any time.

8.0 STATISTICAL AND DATA CONSIDERATIONS

8.1 POWER CALCULATIONS

As a noninferiority study, this trial has been powered to ensure that the lower limit of the 95% confidence interval does not cross the pre-specified noninferiority margin if the null hypothesis is rejected. We have made several conservative assumptions to ensure that the lack of a finding of noninferiority is not due to a lack of statistical power: we assumed a statistical power of 95% (very high power to increase the likelihood that the lower bound of the one-sided 95% CI will be on the null side of the noninferiority margin if usual care without an ACC is truly noninferior to use of an ACC), we have used a one-sided 95% CI of 0.025, and the variance estimate was obtained from a sample of patients similar to those intended for recruitment from the SLN Medical Center.

Special care was taken in establishing the noninferiority margin. Note that the goal of this study is not to demonstrate noninferiority in an absolute clinical sense, but to provide sufficient information to the orthopedic community in order to inform the decision regarding placement of ACC's. This insight led the PI (Dr. Hinman) to conduct an e-mail poll of his colleagues, asking for their perception of the MCID that would lead to a change in practice with respect to placing ACC's. Dr. Hinman received 19 replies with the following response distribution:

0.5 points: 1 (5.3%)
1.5 points: 2 (10.5%)
2.0 points: 11 (57.9%)
3.0 points: 4 (21.1%)
4.0 points: 1 (5.3%)
Mean: 2.18 points / Median: 2.0 points

Given the median MCID of 2 points, we originally chose a conservative value of 1.5 points (0.5 points below the median) for this trial, in order to maximize credibility of the results. This value was revised upward to 2.0 (see below) in version 1.1 of the protocol.

The following describes the methods and assumptions used for calculation of the necessary sample size for this study (power calculations were performed with the PASS power-analysis package (33)):

H_0: The mean NRS pain score in the active-treatment group is less than the mean NRS pain score in the control group on the second postoperative day
H_A: The mean NRS pain score in the active-treatment group is not less than the mean NRS pain score in the control group on the second postoperative day
α: 0.025 (1-tailed) [standard practice for noninferiority trials (34)
β: 0.02 (Power=98%)
Standard deviation = 2.64 (from an interim analysis of the blinded data of 98 enrolled participants)
Noninferiority margin (δ) = 2.0 points
Randomization ratio: 1:1
Test on which calculations based: z-test
Number of evaluable randomized participants required = 60 per group; Total number required = 120
Total number of recruited participants required accounting for 10% withdrawals = 132 (66 per group)

This sample size will require recruitment of 132 participants/64.5 weeks = 2.1 participants per week (the SLN Medical Center orthopedics group performs approximately 20 TKAs per week).

Note on interim data examination to resize the trial: The sample size calculations described above relied on an estimate of the standard deviation of the primary outcome, which was calculated using a sample of 163 KPNC SLN members who underwent TKA in 2018. Although we expect that the standard deviation of the primary trial outcome will align with the estimates used in the sample size calculation, deviations in the estimate used may have a substantial impact on sample size and power. Because of this, we plan to estimate the standard deviation of the primary outcome using interim data mid-way through the trial (the first 59 patients pooled from both trial arms) (35), and will re-calculate the sample size to ensure that our original calculations are reasonably appropriate to the observed

variance. Note that there is no inter-group comparison and, therefore, no cost to the experimentwise alpha.

Note on the revised calculations: Blinded study data were examined twice, most recently after 98 participants were enrolled and the assumed standard deviation of 2.04 was revised upward to 2.64 based on this analysis. In addition, the survey of knee-arthroplasty specialty KPNC orthopedic surgeons conducted by the Principal Investigator showed that 84% of the 19 respondents would set the noninferiority margin at 2.0 points or more. In the original power calculations, we assumed a noninferiority margin of 1.5 points, in order to be highly conservative. However, after further reflection and sensitivity analyses, we found that adopting such a strict noninferiority margin could substantially impair our ability to declare noninferiority for an observed nonzero difference. Therefore, we reset the noninferiority margin back to 2.0 points, consistent with the responses to the orthopedist survey. Finally, in order to retain a very high likelihood of affirming noninferiority if the point estimate of the between-group difference in the outcome pain scores was less than the noninferiority margin, we decreased the beta to 0.02 (power = 0.98).

8.2 STATISTICAL ANALYSIS PLANS

We will summarize baseline variables and covariate data using standard descriptive statistics (frequencies and proportions for categorical variables; means, standard deviations, quartiles, the minimum and maximum for continuous variables). This will allow us to identify baseline imbalances that are due to random chance and possible missing data.

The primary analysis is a comparison of mean NRS pain scores between the two treatment groups at the second postoperative day. This analysis will be conducted with a linear regression model that includes an indicator variable for the usual care without ACC group (the test on the coefficient, denoted β_1, of which will form the primary comparison of interest), and covariates identified as poorly balanced at baseline (i.e., a 20% between-group difference, in general). Note that β_1 represents the difference in mean NRS pain score at the second postoperative day between the usual care without ACC group and use of ACC group, holding all other covariates fixed. The null hypothesis for the test of noninferiority assumes that the usual care without ACC is inferior to the use of ACC (specified in Section 8.1); in terms of the linear regression model, this corresponds to H0: $\beta_1 \geq \delta$, where δ is the pre-specified noninferiority margin of 2.0. The alternative hypothesis assumes that the usual care with ACC is noninferior to the use of ACC, HA: $\beta_1 < \delta$. Noninferiority is established at the $\alpha=0.025$ level if the upper bound of the 95% confidence interval lies below the noninferiority margin, $\delta = 2.0$. The primary analyses will be conducted under the principle of intention-to-treat, which is, admittedly, controversial as some authorities assert that intention-to-treat is non-conservative in the setting of a noninferiority trial (36); missing data will be imputed using a standard multiple-imputation algorithm. As a secondary analysis, we will also repeat the primary analyses under a per-protocol paradigm. Finally, since the NRS is a fundamentally ordinal scale, we will verify the bivariate comparison with a non-parametric Wilcoxon rank-sum test that requires no distributional or linear-scale assumptions. All analyses will be conducted with updated versions of the SAS (37) and Stata (19) statistical packages.

For our secondary aims, we will use the following analytic approaches:

Secondary Aim 1: The first secondary analysis is a comparison of the mean NRS pain scores between the two treatment groups over the two-week follow-up period. We will have up to 15 measurements per individual (daily pain scores over a two-week period including baseline measurement). We are primarily interested in whether the rate of change in NRS pain score over the two-week follow-up period differs between the two treatment groups. These analyses will be conducted with linear mixed-effects models (38,39) that include terms for the effects of time, study group and the group-by-time interaction which will serve as the primary statistical test of the study hypothesis. Subjects will be included as random effects, and the within-subject correlation will be modeled appropriately. The most appropriate error structure will be chosen by comparing model fit using Akaike's Information Criterion (40). The overall difference between two total response curves will be tested with likelihood-ratio tests. The predicted

(modeled) change in the outcome over the relevant follow-up period will be obtained from each model along with the associated standard errors from which 95% confidence intervals will be constructed.

Secondary Aim 2: The mean difference in two-week postoperative opioid use (measured in total morphine equivalents) between the two treatment groups will be compared with a two-sample t-test. A secondary analysis will be conducted with a multiple linear regression model with an indicator variable for treatment group (for which the test of $\beta_1=0$ will form the primary hypothesis test) and adjustment for baseline covariates, use of opioids at baseline, and baseline NRS pain score.

Secondary Aim 3: The frequencies of complications related to ACC will be summarized with proportions and associated exact 95% confidence intervals.

Secondary Aim 4: To identify candidate predictors of differential response to the ACC, we will consider including interaction terms between the treatment indicator and demographic variables and baseline pain NRS scores in the primary linear regression analysis.

8.3 DATA QUALITY CONTROL

All data collected for this trial will be stored in REDCap, a secure, web-based data collection application that employs full range and logic checking (and that is currently in use at KPNC DOR). Study investigators and staff will review data reports bi-weekly to ensure that data collection is proceeding appropriately. Extensive pilot testing of all procedures (from recruitment to data entry) will be completed prior to enrolling participants into the full trial.

Dr. Adrian Hinman, as the facility-based PI, is responsible for the overall implementation and conduct of the study and takes primary responsibility for all clinic-related activities. Dr. Avins, who is based at the KPNC DOR, will take primary responsibility for all data coordination and reporting. All study staff will have regular face-to-face meetings at DOR during which all issues related to study progress will be discussed and procedures refined and documented. The study statistician and programmer/analyst will prepare bi-weekly reports of all critical information including recruitment rates and targets, visit and intervention adherence, completeness of data collection, serious and non-serious adverse events, and all protocol violations and deviations. Reports of incomplete data will be reviewed by the study team on a regular basis to ensure that data acquisition is complete, accurate, and proceeding on schedule. Any evidence of systemic problems in data collection will be resolved quickly.

8.4 DATA AND SAFETY MONITORING PLAN

All data and safety issues will be reviewed by all study investigators and study staff at each biweekly staff meeting.

A single Data and Safety Monitor (DSM) will be appointed for this trial. In order to avoid conflicts of interest, the DSM will not be a KPNC employee and will not have collaborated directly with any study investigators in the past. The DSM will provide written approval of all study procedures and documents (including the content of the regular DSM reports and tables) prior to study initiation. It is anticipated that formal DSM meetings with the study investigators will occur via teleconference prior to study enrollment (to approve all procedures and documents), then at roughly six-month intervals to review all safety and data-related information. Changes to the meeting intervals can be made at any time at the DSM's discretion. A DSM report will be prepared prior to each meeting; this report will include both blinded and unblinded data if requested by the DSM. Adverse-event monitoring and withdrawal of participants are discussed above (Sections 7.1 - 7.3). A full Data and Safety Monitoring Plan is contained in a separate study document.

9.0 ETHICAL CONSIDERATIONS

9.1 INFORMED CONSENT

The principles of informed consent described in Food and Drug Administration (FDA) regulations (21CFR part 50) will be followed. IRB approval of the protocol and the consent form will be given in writing. This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB and the DSM. Written informed consent will be obtained from the participant, who will be given ample time to study the document and encouraged to ask questions during the telephone consent procedure. The informed consent will describe the purpose of the study, the procedures to be followed and the risks and benefits of participation. The participant will retain a copy of the consent form, the HIPAA authorization form, and the Research Subject's Bill of Rights.

9.1 PROCEDURES FOR OBTAINING CONSENT

If the patient expresses interest in potentially enrolling in the study at their first clinic visit, an appointment will be made for a telephone visit with the study Physician's Assistant. At the appointed time, the study PA will call the patient at home and present the study details to the patient using an IRB-approved script and answer any questions the patient may have. The PA will be sure to emphasize that participation is entirely voluntary and that there is no obligation to participate. If the patient expresses a desire to enroll in the study, the PA will ask the patient to retrieve the consent and HIPAA Authorization forms from the clinic study packet; the PA will then walk through all elements of the consent form with the patient, again using an IRB-approved telephone script. If, after this procedure, the patient is still interested in enrolling in the study, they will sign their copy of the consent form. The same procedure will then be repeated for the HIPAA authorization form. The PA will then ask the patient to put both sign forms in the postage-paid reply envelope and mail them back to the orthopedics department at the SLN Medical Center. When these forms are received, the PA will then sign both forms and enter the consent note on the patient's electronic medical chart. The forms will then be set aside in a consistent location for retrieval by the study Project Coordinator or Research Assistant. The forms will be scanned into the patient's electronic medical record and the hard copy will be stored in a locked file cabinet in a secure area at the Division of Research. If the PA is unavailable, any study investigator with a clinical license may conduct the consent procedure.

9.2 CONFIDENTIALITY

Data will be collected on paper forms (including the two-week pain and medication diary) and entered into a REDCap database. REDCap is a fully HIPAA and 21CFR Part 11 compliant data collection application and maintains a high level of security and confidentiality for the study data. Study data can only be accessed through a secure password-protected server with access permissions limited to study personnel and with nightly redundant backups. All accessing of and changes to the data are audited and recorded. Data will be stored on secure servers located behind a firewall at the KPNC DOR with nightly redundant backups. All computers used to access the KPNC intranet will follow standard access-protection procedures, including regular changing of passwords and formation of an audit trail; prior to conduct of the study, all procedures will be tested to ensure that the implemented security procedures cannot be circumvented or defeated. All study personnel will undergo required HIPAA training (certification of successful completion of HIPAA training is a requirement for employment at KPNC).

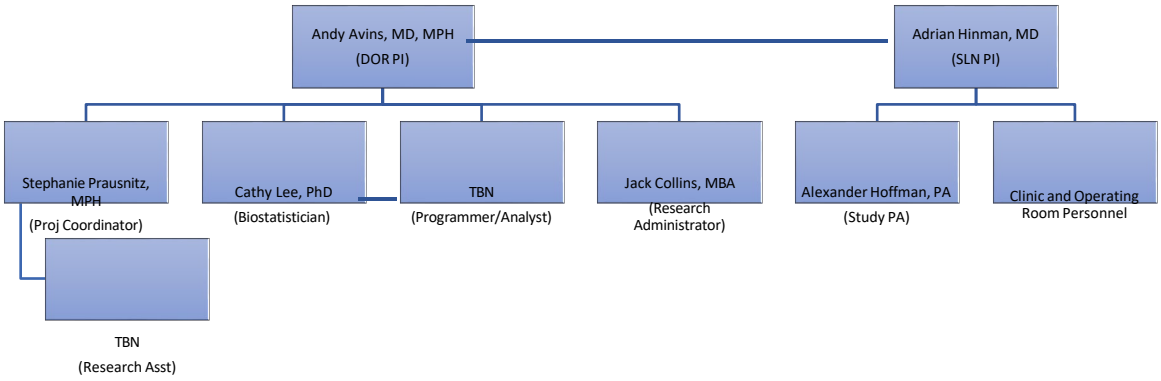
The study data collected on paper forms will be stored in locked file cabinets in a secure location at the KPNC Division of Research. Only authorized study personnel will have access to the file cabinets, which are located in secure sections of the DOR, behind locked doors requiring electronic card access.

Protected Health Information (PHI) will be closely guarded and never shared with individuals outside of the research staff, unless compelled to do so by regulation or law. Such data include any study-related forms that contain any of the 18 HIPAA identifiers. No PHI will be disclosed in any publications or presentations as a result of the work from this study. No PHI will be used in the analysis datasets, as it is not necessary (conforming to the "minimum necessary" standard).

10.0 STUDY ADMINISTRATION

10.1 ORGANIZATIONAL CHART

The organizational and reporting structure of the project is shown below:



10.2 CLINICAL SITE: KPNC SAN LEANDRO MEDICAL CENTER

The Orthopedics Department in the KPNC San Leandro Medical Center is located on the fourth floor of the Medical Center at 2500 Merced St. in San Leandro, CA. The Department is a referral center for TKA surgery and performs approximately 1300 primary TKAs annually. Twelve TKA surgeons from 3 Kaiser Permanente hospitals (San Leandro, Oakland, Fremont) perform TKA surgeries in the San Leandro Hospital operating rooms.

The outpatient clinic in San Leandro is physically attached to the hospital and consists of offices for 9 full-time orthopedic surgeons, 4 of whom are TKA surgeons. These offices are also shared with 2 non-operative physicians, 8 physician assistants, 9 medical assistants and one office manager. One hundred and fifty to two hundred patients per day are routinely seen for a variety of conditions within the scope of orthopedic and sports medicine. Office space is shared with the Podiatry department. All orthopedic diagnostic and treatment procedures are included in the scope of practice, including appropriate medications and interventional procedures. A close working relationship exists with the Department of Radiology.

10.3 DATA COORDINATING CENTER: KPNC DIVISION OF RESEARCH

The Data Coordinating Center resides at the Division of Research, Northern California Kaiser Permanente in Oakland, California. The data-related activities of the ACCESS trial will be supervised by the Dr. Avins (co-PI), Dr. Lee (Biostatistician), and Ms. Prausnitz (Project Manager). The Coordinating Center will take responsibility for monitoring recruitment and data quality; regular reports of recruitment and issues related to data quality will be produced for monthly project meetings. In addition, the Data Coordinating Center will have responsibility for ensuring timely reporting of adverse event data, preparation of reports for the DSM, and IRB renewals. As all data collection will be centralized at the Division of Research, the Coordinating Center will ensure that all data collection forms and systems are working appropriately.

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APPENDIX 1: SCHEDULE OF EVALUATIONS

VISIT: **PROCEDURE**:	Initial clinic visit	Telephone consent call*	Preop call	Day of surgery	Daily patient diary	2-day postop call	2-week postop call*	3-month EMR data extraction
Introduction to study	X	X						
Provision of information packet	X							
Eligibility screening		X	X					
Informed consent		X						
Randomization				X				
DATA COLLECTED								
Demographics		X						
Clinical history		X						
Numerical rating pain scale		X	X			X	X	
PROMIS-10			X				X	
KOOS Jr			X				X	
Analgesic use assessment			X					
Daily pain/medication diary					X			
Adverse Event Assessment						X	X	X

Key:
EMR = Electronic Medical Record
Postop = Postoperative
Preop = Preoperative

*Several items (Demographics, Clinical History, Numerical rating pain scale, PROMIS-10, KOOS Jr, Analgesic use assessment) will be collected by the participant at home on a paper questionnaire and mailed to the DOR; participants will be reminded to do so during the Telephone consent call and at the 2-week closeout postop call.

APPENDIX 2: KEY PERSONNEL

Adrian Hinman, MD
Co-Principal Investigator
Orthopedics
KPNC San Leandro Medical Center
2500 Merced St
4th Floor
San Leandro, CA 94577
Phone: (510) 454-7292
E-mail: Adrian.D.Hinman@kp.org

Andrew L. Avins, MD, MPH
Co-Principal Investigator
Research Scientist
KPNC Division of Research
2000 Broadway
Oakland, CA 94612
Phone: (510) 891-3557
Fax: (510) 891-3606
E-mail: andy.l.avins@kp.org

Kasey Cortese, MD
Co-Investigator
Chief, Orthopedics
KPNC San Leandro Medical Center
2500 Merced St
4th Floor
San Leandro, CA 94577
Phone: (510) 454-7295
E-mail: Kasey.D.Cortese@kp.org

Bejoy Thomas, MD
Co-Investigator
Anesthesia
KPNC San Leandro Medical Center
2500 Merced St
San Leandro, CA 94577
Phone: (510) 913-4859
E-mail: Bejoy.G.Thomas@kp.org

Catherine Lee, PhD
Biostatistician
Kaiser Permanente Division of Research
2000 Broadway
Oakland, CA 94612 -2304
Phone: (510) 891-3556
Fax: (510) 891-3606
E-mail: catherine.lee@kp.org

Stephanie Prausnitz, MS
Project Manager
KPNC Division of Research
2000 Broadway

Oakland, CA 94612 -2304
Phone: (510) 891-3601
Fax: (510) 891-3606
E-mail: Stephanie.R.Prausnitz@kp.org

Alexander Hoffman, PA-C
Orthopedics
KPNC San Leandro Medical Center
2500 Merced St
4th Floor
San Leandro, CA 94577
Phone: (510) 454-7317
E-mail: alexander.e.hoffman@kp.org