UNIVERSITY of SOUTH FLORIDA
Research & Innovation

PROTOCOL TITLE:

Use of Smart Knee Implant to Evaluate Efficacy and Superiority of Liposomal Bupivacaine and Bupivacaine with Meloxicam in Early TKA recovery

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

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1.0 Study Summary

Study Title	Use of Smart Knee Implant to Evaluate Efficacy and Superiority of Liposomal Bupivacaine and Bupivacaine with Meloxicam in Early TKA recovery
Study Design	Single-center, single surgeon, single-blind, randomized, prospective comparative study. Participants undergoing primary unilateral TKA receive a periarticular injection of either Exparel, Zynrelef, or bupivacaine hydrochloride alone, and are followed for the first 2 years.
Primary Objective	To compare the rate of early functional recovery during the first 3 postoperative days, measured as the change/improvement over time in objective gait metrics and daily total qualified step count, between the Exparel group, Zynrelef group, and the bupivacaine hydrochloride alone group.
Secondary Objective(s)	To compare the rate of improvement in knee/functional range of motion (ROM) at 1 week post-operatively; early postoperative pain scores (VAS/numeric), cumulative opioid consumption (oral morphine equivalents), and PROMs up to two years post-operatively; and to explore whether age, sex, and BMI modify early recovery within and across groups. To compare the relative cost of injection for patients.
Research Intervention(s)	n/a
ClinicalTrials.gov NCT #	n/a
Study Population	Adults undergoing primary unilateral total knee arthroplasty for end-stage osteoarthritis who provide informed consent.
Sample Size	183 total Patients – 61 in the Liposomal Bupivacaine group, 61 in the Bupivacaine with meloxicam group, and 61 in the Bupivacaine Hydrochloride alone group
Study Duration for Individual Subjects	Primary outcome within the first 72 hours post-operatively. Secondary outcomes to the first two postoperative years
Study Specific Abbreviations/ Definitions	TKA – Total Knee Arthroplasty; LB – Liposomal Bupivacaine (Exparel); BH – Bupivacaine Hydrochloride; PAI – Periarticular Injection/Infiltration; ROM – Range of Motion; VAS – Visual Analog Scale; OME – Oral Morphine

	Equivalent; PROM – Patient-Reported Outcome Measure; EHR – Electronic Health Record; KOOS – Knee Injury and Osteoarthritis Outcome Score; KSS – Knee Society Score; "early recovery rate" – the change in an objective activity/gait metric, daily total step count, or ROM across the first 3 postoperative days (e.g., slope of improvement or change from the earliest postoperative measurement to day 3).

2.0 Objectives

2.1 The primary objective is to compare the rate of early functional recovery during the first 3 postoperative days, measured as the change/improvement over time in objective gait metrics and daily total qualified step count, between patients undergoing primary unilateral TKA who receive periarticular liposomal bupivacaine (Exparel), bupivacaine mixed with meloxicam (Zynrelef), and those who receive bupivacaine hydrochloride (Marcaine) alone. The 72-hour primary endpoint reflects the pharmacologic window of the study injections, whose analgesic efficacy is greatest in the first three postoperative days and wanes thereafter, making this the interval most sensitive to any between-arm difference.

2.2 Secondary objectives are to compare: (a) the rate of improvement in knee/functional range of motion (ROM) over the first postoperative week; (b) early postoperative pain scores (VAS/numeric) across the first 1 week, 2 weeks, 6 weeks, 3 months, one year, and two years; (c) cumulative opioid consumption expressed as oral morphine equivalents; (d) the influence of patient factors (age, sex, BMI) on early functional recovery within and across groups; (e) PROMs up to two years post-operatively; and (f) the relative cost of injection for patients.

2.3 The authors hypothesize that patients randomized to receive either liposomal bupivacaine or bupivacaine mixed with meloxicam will demonstrate a faster rate of early functional recovery and earlier cessation of postoperative pain during the first 3 post-operative days than patients who receive bupivacaine hydrochloride alone, reflecting both the prolonged analgesia attributed to the liposomal formulation in Exparel and additional benefits of meloxicam in Zynrelef.

3.0 Background

3.1 Total knee arthroplasty (TKA) is a common and successful procedure for end-stage knee osteoarthritis, but more than half of patients report substantial acute postoperative pain, which can impair early mobilization and functional recovery. Effective, opioid-sparing local analgesia is therefore a priority, particularly as primary TKA has shifted toward outpatient and same-day care following the removal of primary TKA from the Medicare inpatient-only list in 2018 and the acceleration of this trend during the COVID-19 pandemic.

3.2 Periarticular injection of local anesthetic at the time of surgery is a standard component of multimodal analgesia. Liposomal bupivacaine (Exparel) is a liposome-encapsulated formulation designed to provide a prolonged sensory block through extended release and is licensed for single-dose periarticular infiltration in the knee. However, the comparative evidence is mixed.[1] A large multicenter, patient-blinded randomized clinical trial (the SPAARK trial, 533 participants) found no difference between liposomal bupivacaine and bupivacaine hydrochloride alone in the coprimary outcomes of Quality of Recovery (QoR-40) at 72 hours or pain VAS area under the curve from 6 to 72 hours, and found no difference in cumulative opioid consumption or in functional outcomes at 6 weeks, 6 months, or 1 year.[2] Most prior randomized trials were smaller and used heterogeneous comparators, with only isolated studies reporting a benefit.[3] Evidence on functional recovery is similarly divided: some comparative studies report that liposomal bupivacaine is associated with earlier achievement of gait and

ambulation milestones, whereas pooled meta-analytic data have found no significant difference in range of motion, ambulation distance, or length of stay.[4,5]

3.3 An additional injection has been developed recently, combining bupivacaine with meloxicam (Zynrelef). Clinical studies have shown Zynrelef to reduce pain and opioid consumption in the immediate post-operative period.[6-8]

3.4 Separately, objective measurement of postoperative activity is now feasible. Recent work using an implanted tibial sensor (794 patients) demonstrated that objective gait metrics, such as qualified step count, cadence, walking speed, stride length, and functional range of motion, can be collected during activities of daily living.[9] Activity in this period is very low and rises steeply: median daily qualified step count was approximately 42 at week 1 and increased markedly over the following weeks, with recovery trajectories differing by sex and BMI. Because patients are far from their preoperative baseline at one week, the clinically relevant and measurable quantity in the first postoperative week is the rate of early improvement rather than return to baseline.

3.5 Objective metrics, together with documented ROM and functional notes, provide a less subjective basis for quantifying early recovery than patient-reported measures alone.[10] Despite the prior randomized evidence, periarticular anesthetic choice continues to vary in practice. If liposomal bupivacaine or bupivacaine mixed with meloxicam confers an early analgesic advantage, they would be expected to produce faster early mobilization, a question best examined prospectively in the first 3 days postoperatively using objective activity data, and one that has received limited direct study. This prospective study will collect clinical and objective activity/recovery data over the first 3 postoperative days to compare early recovery rate between the three periarticular regimens. It will also look at post-operative pain scores, rate of improvement, and opioid consumption at 1 week, 2 weeks, 6 weeks, and 3 months, one-year, and 2 years post-op.

4.0 Safety Endpoints

4.1 The primary safety endpoint is the incidence of adverse events (AEs) and serious adverse events (SAEs) through the follow-up period, compared across the three treatment arms (liposomal bupivacaine [Exparel], bupivacaine/meloxicam [Zynrelef], and bupivacaine hydrochloride [Marcaine]). All events will be graded for severity and assessed for their relationship to the study intervention.

4.2 Secondary safety endpoints include the incidence, by arm, of the following:

Local anesthetic-related effects, including injection-site reactions and any transient local numbness or weakness in the operative limb.

Wound-healing and surgical-site outcomes, consistent with routine postoperative assessment.

Opioid-related side effects commonly monitored after knee replacement, such as nausea, sedation, or constipation.

Tolerability of the meloxicam component in the Zynrelef arm, including gastrointestinal and renal parameters, consistent with standard NSAID monitoring.

Standard perioperative safety events captured as part of routine care, including thromboembolic events and falls during early mobilization.

Overall complication and readmission rates, recorded through the standard postoperative follow-up period.

All adverse events and serious adverse events will be recorded from the time of study-drug administration through the end of the follow-up period. Each event will be graded for severity and assessed for its relationship to the study intervention, and will be reported in accordance with institutional and IRB safety-reporting requirements and the study's safety-monitoring plan.

Because the Zynrelef arm contains an NSAID (meloxicam), its safety profile differs from that of the liposomal bupivacaine and control arms. Safety monitoring will account for this asymmetry, and patients with contraindications to NSAIDs will be excluded per the eligibility criteria.

As all three arms of this study have already been approved by the FDA, we expect there to be minimal risk to these adverse events.

5.0 Study Intervention

The study intervention being evaluated is whether periarticular liposomal bupivacaine (Exparel) and bupivacaine with meloxicam (Zynrelef) produce faster early functional recovery during the first three postoperative days compared with bupivacaine hydrochloride (Marcaine) alone in patients undergoing primary unilateral TKA. At the time of surgery, each enrolled participant receives a periarticular injection of either (a) liposomal bupivacaine (b) bupivacaine mixed with meloxicam, or (c) bupivacaine hydrochloride alone. Participants are followed through the first two postoperative years, during which pain scores, PROMs, and opioid use are recorded. For only the first post-operative week, gait/activity, daily total step count, knee ROM, and other gait metrics are recorded. The primary objective is the change in gait metrics observed in the first 3 postoperative days.

Devices	**Drugs/Biologics**
☐ FDA Approved Device – Approved Use	☒ FDA Approved Drug/Biologic – Approved Use
☐ FDA Approved Device – Unapproved Use	☐ FDA Approved Drug/Biologic – Unapproved Use
☐ Investigational Device – Non-Significant Risk	☐ Investigational Drug/Biologics
☐ Investigational Device – Significant Risk	☐ Placebo
☐ Humanitarian Use Device Exemption	☐ Other Drugs/Biologics

☐ Other Devices	

5.2 The investigational drugs (Exparel, Zynrelef, Marcaine) are FDA-approved agents used within their approved labeling for postoperative pain management and are not manufactured, reconstituted, or altered by study personnel. Drug control and accountability will be managed by the hospitals' intuitional policy

5.3 N/A

5.4 The study intervention being evaluated is whether periarticular liposomal bupivacaine (Exparel) and bupivacaine with meloxicam (Zynrelef) produce faster early functional recovery during the first three postoperative days compared with bupivacaine hydrochloride (Marcaine) alone in patients undergoing primary unilateral TKA.

5.5 The drugs under investigation are FDA approved. Storage and dispensation of the medication is as per standard of care.

6.0 Procedures Involved

6.1 This is a prospective, single-center, single-surgeon, single-blind comparative study of patients undergoing primary unilateral TKA. Eligible patients are approached, consented, and enrolled before surgery. At the time of surgery, each participant receives a periarticular injection of either liposomal bupivacaine, bupivacaine mixed with meloxicam, or bupivacaine hydrochloride alone as part of surgical care and is followed through the first 2 postoperative years. The study is conducted by the principal investigator and delegated research team members.

6.2 Please select the methods that will be employed in this study (select all that apply):

☐ Audio/Video Recording	☐ Psychophysiological Recording
☐ Behavioral Interventions	☐ Record Review - Educational
☐ Behavioral Observations and Experimentations	☐ Record Review - Employee
☐ Deception	☒ Record Review- Medical
☐ Focus Groups	☐ Record Review - Other
☐ Interviews	☐ Specimen Collection or Analysis
☐ Investigational Device – Non-Significant Risk (e.g. Mobile Applications)	☒ Surveys and/or Questionnaires
☐Psychometric Testing	☐ Other Social-Behavioral Procedures

- The research-related portion of the study is the prospective comparison of early functional recovery between the three periarticular analgesia groups (liposomal

bupivacaine versus bupivacaine mixed with meloxicam versus bupivacaine hydrochloride alone) and the collection of gait metrics for the first postoperative week and pain, PROMs, and opioid data during the first two postoperative years.

- An additional research related portion of the study is the randomization between three cohorts which are the liposomal bupivacaine versus bupivacaine mixed with meloxicam versus bupivacaine hydrochloride alone cohort. This will be a single-blind study in which the patients will not be told their group. The attending surgeon/PI will know the group, though, as they will be the one to administer the injection. Randomization method: Subjects will be assigned to one of three treatment groups (Group A, Group B, Group C) in a 1:1:1 ratio using permuted block randomization with a fixed block size of 3. Within each block, the three group assignments are randomly ordered to ensure that after every three enrollments, each group has received exactly one subject. The randomization list will be maintained by the unblinded study coordinator and will not be accessible to enrolling investigators or study staff involved in patient assessment. Assignments will be revealed sequentially only at the time of enrollment.
- Another research related activity is the requirement of patients to follow up for 24 months post-operation. Patients will fill out the PROMs forms at their post-op visit. These PROM forms will be available for the patient to fill out in person.

Accessing and/or collecting data:

- Data collected will include:
    - Patient name, MRN, age, sex, body mass index, and comorbidities;
    - Surgical and procedural data (date of surgery, laterality, ASA classification, operative time, implant used, anesthetic technique, and details of the periarticular injection administered);
    - Pre-operative timed up and go test
    - Analgesia exposure (periarticular agent and dose, and additional multimodal analgesia);
    - PROMs and opioid outcomes
        - VAS/numeric pain scores
        - KOOS
        - KSS
        - UCLA Activity Score
        - Tegner Activity Scale
        - EQ-5D-5L Quality of Life
        - Cumulative opioid consumption as oral morphine equivalents
    - Functional recovery and activity metrics over the first 7 postoperative days (daily total/qualified step count and objective gait data where available, including cadence, distance, walking speed, stride length, functional knee/tibial ROM, and documented knee ROM), with date/time of each measurement to allow calculation of recovery rate.
        - Any available preoperative reference values will be recorded for context.
    - Kellgren-Lawrence Score
    - Cost of injection

- Data will be obtained prospectively from enrolled participants at baseline and during the first 2 postoperative years. The principal investigator and delegated research team members have clinical authority to access participant records at the study institution. Supporting operative, therapy, and clinical notes are obtained from the institutional EMR. Data will be entered into a secure database by delegated research staff.

6.3 The injections used are already part of standard of care. VAS, KOOS, and KSS are also PROMs that are routinely collected. For the sake of this research study, UCLA, Tegner, and EQ-5D-5L will also be collected. The implant used during surgery is also already part of standard of care and the metrics are routinely available. Study visits occur at the same time as standard of care visits and will be conducted in a closed room to ensure confidentiality. Study information will not be shared beyond the authorized study personnel.

6.4 Only members of the research team will have access to the medical records and the surveys filled out by patients. There is minimal risk to data breach as all patient info is stored on a secure research folder.

6.5 The principal investigator has research credentials at the Florida Orthopaedic Institute (FOI) and authority to access the data.

Athena (FOI outpatient EMR system) will be used for additional information to find the data points mentioned above.

7.0 Data and Specimen Storage for Future Research

7.1 N/A.

8.0 Sharing of Results with Subjects

If subjects ask for their data, they will be given only their data. Otherwise, the results will not be shared with people outside of the research study.

9.0 Study Timelines

Patients participating in the research study are assessed at the preoperative (enrollment) visit and then followed through the first 2 postoperative years, during which gait/activity, daily total step count, knee ROM, pain scores, and opioid use are recorded. Routine postoperative clinical follow-up continues per standard of care.

	Baseline (Pre-Op)	3 days post-op	7 days post-op	2 weeks post-op	6 weeks post-op	3 months post-op	1 year post-op	2-year post-op
Screening	x							
Randomization	X							

Informed Consent	x							
Demographics	x							
Periarticular Injection	x							
Gait / Step Count / ROM	x	X	X					
Pain Scores / Opioid Use/ PROM Questionnaires	x	X	x	x	x	x	x	X
Complications		x	x	x	x	x	x	x

10.0 Inclusion and Exclusion Criteria

10.1 Individuals will be screened for eligibility at their initial pr-operative visit. If they meet the below inclusion criteria, and are willing to participate in the study, a research coordinator will explain to the patient the attached consent form.

10.2 Inclusion criteria:

- Adults between the age of 18 and 90 years old.
- Scheduled to undergo primary unilateral total knee arthroplasty for symptomatic end-stage osteoarthritis, with the Persona IQ implant.
- Timed Up and Go (TUG) Test <20 seconds
- Planned to receive a periarticular injection of either liposomal bupivacaine, bupivacaine mixed with meloxicam, or bupivacaine hydrochloride alone as part of surgical care.
- Willing and able to provide written informed consent and to complete the first-week assessment schedule.

10.3 Exclusion criteria:

- Revision or unicompartmental-only knee replacement.
- Diabetes with A1c >7.5
- Morbid obesity with BMI >40 kg/m^2
- Chronic opioid use
- PJI/Infection
- Documented allergy or intolerance to amide-type local anesthetics.
- Severe inflammatory arthropathy (e.g., rheumatoid arthritis) with more than 4 joints affected.
- Objective evidence of nerve damage in the affected limb, or another condition precluding the assessments or the intervention.

- Inability to provide informed consent or to complete the first-week assessments; or concurrent enrollment in another interventional drug trial.

10.4 Following the start of the study, there are minimal factors that may deem a patient ineligible. Loss of follow-up and the patient's own decision to withdraw are the only foreseeable events.

10.5 USF students/employees, socially or economically disadvantaged patients or wards of the state will not be targeted for this study.

11.0 Vulnerable Populations

11.1 Vulnerable patients will not be included in this study.

12.0 Local Number of Subjects

To power this study, we used an ANOVA test. Effect size was determined based on a previous study by Cushner, et al. that used a tibial implant to track gait metrics. For their study, the average step count was 289 at week 1 with a standard deviation of 608 steps. For our 3 groups, we assume the Exparel and Zynrelef groups will provide patients enough relief to double their step count compared to Marcaine (600 vs 600 vs 300 steps). This gives an effect size f of 0.2326009. When calculating for a power of 0.8, α alpha error probability of 0.05, and *a priori* power analysis, the proposed sample size is 183 patients, or 61 per group. Assuming a drop-out rate of 10%, we plan to recruit 200 patients.

13.0 Recruitment

The principal investigator/surgeon will screen for inclusion/exclusion criteria at the patient's preoperative evaluation and give a general synopsis of the study. If the patient is eligible and interested, the clinic research coordinator will be notified to explain the study in detail and obtain informed consent before the day of surgery.
Patients are screened for eligibility (see sections 10.1 and 10.2) at the preoperative evaluation by the principal investigator, which does not require study members to review medical records or clinic schedules for potential patients.

☐ Email	☐ Record Review
☐ Flyer	☐ SONA
☐ Letter	☐ ResearchMatch (must upload HRP-500 template)

☐ News Advertisement	☒ Other: Initial Evaluation Appointment described in 12.2
☐ Online/Social Media Advertisement	

14.0 Withdrawal of Subjects

There are no anticipated circumstances under which subjects will be withdrawn from the research without their consent, since eligibility is determined at the preoperative evaluation with the surgeon/principal investigator.

Subjects can notify staff about withdrawal from the study. Data already collected will be kept confidential until study completion. Subjects can continue to follow up with the surgeon for routine standard-of-care TKA management.

15.0 Risks to Subjects

15.1 This is a prospective comparison of three periarticular local anesthetic regimens, all within accepted clinical practice for TKA; the choice between them is the question under study. Foreseeable risks include those associated with the study drugs and the periarticular injection (e.g., transient local numbness or weakness, injection-site reaction, and rare systemic local-anesthetic toxicity) and the general risks of TKA surgery and anesthesia, which are present regardless of study participation. Because liposomal bupivacaine, bupivacaine mixed with meloxicam, and bupivacaine hydrochloride are FDA-approved agents used in standard clinical practice, the incremental risk attributable to study participation is low. There remains a minimal risk of breach of confidentiality inherent to any research involving identifiable health data; this is mitigated by the security measures described in section 17.0.

16.0 Potential Benefits

Participants may or may not receive a direct benefit; whether either regimen yields faster early functional recovery is the hypothesis under investigation and cannot be guaranteed. All participants receive standard high-quality surgical care and standardized multimodal analgesia.

Society may benefit from this study as it will provide objective, activity-based evidence on whether periarticular liposomal bupivacaine and/or bupivacaine mixed with meloxicam accelerate early functional recovery after TKA relative to bupivacaine hydrochloride alone. This information may inform evidence-based, cost-conscious analgesia protocols and opioid-sparing strategies for the large population of patients undergoing TKA annually.

17.0 Data Management and Confidentiality

17.1 Descriptive statistics will be used to summarize patient demographics and outcomes, including means with standard deviations for continuous variables and frequencies with percentages for categorical variables.

To power this study, an a priori power analysis was performed for a one way ANOVA (G*Power 3.1.9.7). Effect size was determined from a previous study by Cushner et al., which used an implanted tibial sensor to track gait metrics and reported a mean daily step count of 289 at week 1 with a standard deviation of 608. For the three groups, we assumed the Exparel and Zynrelef groups would each roughly double the daily step count of the Marcaine (control) group, corresponding to group means of 600, 600, and 300 steps. Entering these means with a common standard deviation of 608 yielded an effect size f of 0.233. With a two sided alpha of 0.05, a power of 0.80, and three groups, the required sample size was 183 patients, or 61 per group. Assuming a dropout rate of 10 percent, we plan to recruit 200 patients. Following a significant omnibus ANOVA, the three prespecified pairwise comparisons (Exparel vs. control, Zynrelef vs. control, and Exparel vs. Zynrelef) will be evaluated with a Tukey adjustment to control the family wise error rate.

17.2 Data will be stored in an institution-approved Research Drive Folder on a secure, password-protected institutional server at the Florida Orthopaedic Institute. Access is restricted to IRB-approved research team members with current CITI and HIPAA training. Role-based access control ensures that only personnel with a specific need can access identifiable data. Data integrity is assured through manual verification by a research coordinator prior to analysis.

Identifiable information collected includes participant names, medical record numbers, dates of birth, and dates of surgery and follow-up visits. These identifiers are stored separately from the analytic dataset and linked only by study ID number. Data will be stored for a minimum of 5 years following study completion per institutional policy. At the end of the retention period, data will be destroyed by secure electronic deletion from all institutional servers. No confidential data will be shared outside the approved research group.

17.3 Protected Health Information (PHI) authorization (select all that apply):

☐ Obtaining Online or Verbal Authorization (Alteration of HIPAA Authorization)	☒ Obtaining Signed Authorization
☐ Waiver of HIPAA Authorization for Entire Study	☐ Data Use Agreement
☐ Business Associate Agreement	

- Participants will provide signed HIPAA authorization as part of the consent process prior to surgery. Authorization will cover access to preoperative clinical records, surgical records, and all study-related outcome data through the first-week follow-up period.
- PHI will not be disclosed to or received from individuals outside of the approved research group. PHI will not be reused or disclosed to any other person or entity except as required by law, for authorized oversight of the research project, or for other research for which use or disclosure of PHI would be permitted by the HIPAA privacy regulations.

- Participants are identified prospectively by the treating surgeons at the preoperative clinic visit; signed authorization is obtained at that time before any research procedures begin.

18.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

18.1 Patients are assigned a study ID at the time they are included into the study and that is used for identification for the remainder of the study. Only authorized study personnel will have access to any study-related files. Study visits occur at the same time as standard of care visits and will be conducted in a closed room to ensure confidentiality. Study information will not be shared beyond the authorized study personnel.

18.2 The study team will obtain consent prior to receiving any information about participants.

19.0 Provisions to Protect the Privacy Interests of Subjects

19.1 Patients are assigned a study ID at the time they are included into the study and that is used for identification for the remainder of the study. Only authorized study personnel will have access to any study-related files. Study visits occur at the same time as standard of care visits and will be conducted in a closed room to ensure confidentiality. Study information will not be shared beyond the authorized study personnel.

20.0 Compensation for Research-Related Injury

This research study is minimal risk and does not deviate from the standard of care protocol for total knee arthroplasty.

21.0 Subject Costs and Compensation

21.1Participation in the study will not accrue additional cost to the patient, since all three periarticular regimens are used within standard clinical care for TKA.

21.2 If you will provide compensation to subjects, select all that apply:

☒ No Compensation	☐ Tokens (pens, food items, etc.)
☐ Financial Compensation (cash, gift cards)	☐ Other
☐ Course Credit (i.e. extra credit, SONA points)	

- n/a

22.0 Consent Process

22.1 Select the consent options that will be used during the course of the study (choose all that apply):

☒ Obtaining Signed Consent (Subject or Legally Authorized Representative)	☐ Obtaining Consent Online (Waiver of Written Documentation of Consent)
☐ Obtaining Signed Parental Permission	☐ Obtaining Verbal Consent (Waiver of Written Documentation of Consent)
☐ Obtaining Signed Assent for Children or Adults Unable to Consent	☐ Waiving Consent and/or Parental Permission (Waiver of Consent Process)
☐ Obtaining Verbal Assent for Children or Adults Unable to Consent	☐ Waiving Assent/Assent is Not Appropriate
☐ Obtaining eConsent Signatures (Subject or Legally Authorized Representative)	☐ Obtaining eConsent Parental Permission
☐ Obtaining eConsent Assent for Children	

22.2 Signed consent will be obtained at the preoperative clinic visit, prior to the day of surgery, by a delegated member of the research team (not the treating surgeon).

- Location: Consent will take place in a private clinic room at the study institution during the pre-operative appointment.
- Waiting period: Participants will be given the consent form before the scheduled surgery date, with the option to review it at home and ask questions by phone or at a pre-surgical check-in.
- Ongoing consent: At each follow-up visit, participants are reminded of their right to withdraw without consequence to their clinical care. Re-consent will be obtained for any protocol amendments per IRB requirements.
- Roles: A trained research coordinator will conduct the consent discussion. The treating surgeons will not lead the consent process to minimize coercion.
- Time devoted: Approximately 20–30 minutes will be devoted to reviewing the consent form, explaining the study, and answering questions.
- Minimizing coercion: Participants are explicitly informed that declining or withdrawing will have no effect on their clinical care or their relationship with their treating surgeon.
- Ensuring understanding: The consenting team members will use teach-back techniques to confirm participant understanding of the study purpose, the two periarticular analgesia options, the first-week assessment schedule, and the voluntary nature of participation.

22.3 N/A - verbal or online consent is not used in this study.

22.4 N/A - all participants provide signed consent. No waiver of consent is requested.

22.5 If non-English-speaking patients are identified, a qualified medical interpreter will be used for the consent discussion. Written consent materials will be translated into the participant's primary language and reviewed by the IRB before use.

22.6 N/A - participants must be 18 years of age or older. No children or individuals requiring a legally authorized representative will be enrolled.

23.0 Setting

23.1 All surgical procedures are performed by a fellowship-trained arthroplasty surgeon at the study institution. The surgeon, who is also the PI, performs surgery at AdventHealth Carrollwood Hospital, as well as the Florida Orthopaedic Institute Cypress Surgery Center. Surgeries will be evenly dispersed between these two locations. Operative and perioperative care, including the multimodal analgesia regimen, follows institutional standard practice. The periarticular injection is administered using a standardized technique.

23.2 Objective gait/activity, daily total step count, and knee ROM are recorded during the first 7 postoperative days using standardized institutional methods using a tibial sensor implant, together with pain scores, PROMs, and opioid consumption documented in the medical record for the first two postoperative years.

23.3 Research data collection and clinical assessments are conducted by delegated research staff at the study institution. Postoperative rehabilitation follows the institution's standard protocol, and recovery milestones are documented at each clinical contact.

24.0 References

[1] Hamilton TW, Athanassoglou V, Mellon S, et al. Liposomal bupivacaine infiltration at the surgical site for the management of postoperative pain. Cochrane Database Syst Rev. 2017;2(2):CD011419. doi:10.1002/14651858.CD011419.pub2

[2] Hamilton TW, Knight R, Stokes JR, et al; for the SPAARK Study Group. Efficacy of liposomal bupivacaine and bupivacaine hydrochloride vs bupivacaine hydrochloride alone as a periarticular anesthetic for patients undergoing knee replacement: a randomized clinical trial. JAMA Surg. 2022;157(6):481-489. doi:10.1001/jamasurg.2022.0713

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