Title: Enhancing pain management for knee replacement patients through an innovative non-invasive and opioid-sparing device (NEUROCUPLE™)

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PROTOCOL TITLE:

Enhancing pain management for knee replacement patients through an innovative non-invasive and opioid-sparing device (NEUROCUPLE™)

PRINCIPAL INVESTIGATOR:

Jacques E. Chelly
Department of Anesthesiology and Perioperative Medicine
412-623-6904
chelje@anes.upmc.edu

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	V.1.1	Changes to the inclusionary criteria	No
2	V.1.2	Change to co-primary outcome, opioid refill, from co-primary outcome to an exploratory outcome. Opioid refill prescription was standardized during the clinical trial with a fixed number of opioid pills prescribed, which hampered the trial. Moreover, it was not an accurate measure of opioid consumption of subjects. Additionally, just a 2-week application of study intervention is unlikely to impact opioid refill outcome at 6 weeks after TKA. Hypothesis and a couple of other outcomes were not explicitly mentioned in the earlier version.	No

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1.0 Study Summary

Study Title	NEUROCUPLE™ in TKA patients
Study Design	Double-blinded randomized (1:1) placebo-controlled clinical trial
Primary Objective	The objective of this clinical trial study is to determine the feasibility and effectiveness of 2-week application of the NEUROCUPLE device for pain relief after TKA
Secondary and exploratory Objective(s)	Analysis will be based on: • Postoperative pain at rest and during movement, • patient functional recovery (range of motion and ability of the patient to walk 30 and 100 ft), • the consumption of postoperative opioid and non-analgesic. • Length of hospital stay • Postoperative nausea and vomiting
Research Intervention(s)/ Investigational Agent(s)	NA
IND/IDE #	NA
Study Population	Patients undergoing Total Knee Arthroplasty (TKA)
Sample Size	156
Study Duration for individual participants	Subjects will participate from enrollment through 6 weeks postoperative discharge.
Study Specific Abbreviations/ Definitions	Total Knee Arthroplasty (TKA) Enhanced Recovery After Surgery (ERAS) Peripheral Nerve Blocks (PNBs) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Transcutaneous Electrical Nerve Stimulation (TENS) Brief Pain Inventory (BPI) Opioid Use Disorder (OUD) Numerical Rating Scale (NRS) Post Anesthesia Care Unit (PACU) Range Of Motion (ROM) Lower Extremity Function Scale (LEFS) Electronic Medical Records (EMR) Personal Identification Number (PIN) Institutional Review Board (IRB) Adverse Event (AE) Protected Health Information (PHI)

2.0 Objectives

The objective of this clinical trial study is to demonstrate the efficacy of NEUROCUPLE™ further clinically as a nonpharmacological postoperative pain relief treatment for individuals recovering from knee replacement surgery.

Specific Aims

Compare the effectiveness of the NEUROCUPLE™ patch versus placebo (patch without capacitors) after knee replacement surgery in a randomized clinical trial in 120 patients at UPMC clinical hospitals with standardized perioperative care.

120 patients will be randomized (1:1 ratio) to a NEUROCUPLE™ (n=60) group and placebo (n=60) before surgery over the one-year study period. Surgery will be performed using the approved enhanced recovery protocol for pain management. Following surgery, either an active NEUROCUPLE™ patch (nCAP group) or a placebo patch (the same patch without nanocapacitors) will be applied over the knee for 14 days. All patients will receive standard of perioperative care including multimodal pain management. Analysis will be based on the postoperative pain at rest and during movement, patient functional recovery (range of motion and ability of the patient to walk 30 and 100 ft), and the consumption of postoperative opioid and non-analgesic.

Milestones:

1) 2-point reduction in postoperative pain (using 0 to 10 pain scale) at rest and with movement in the first week after surgery,
2) >40% reduction in prescription opioid use at week 6 after TKA, and
3) significantly better functional recovery with NEUROCUPLE device versus placebo at weeks 1, 2, and 6.

Hypotheses:

The hypothesis is that NEUROCUPLE will significantly reduce postoperative pain and opioid use compared to sham/placebo device following TKA. Successful completion of this Phase I program will demonstrate effectiveness and superiority of the NEUROCUPLE device as a non-invasive, non-pharmacological alternative to opioids for the treatment of postoperative pain following TKA. This will support the FDA device approval for the indication of postoperative pain relief following TKA and payor reimbursements. In our Phase II STTR, we will expand the indications with a clinical trial testing in different indications such as hip replacement surgery and expand the TKA study population by including patients with psychological disorders and preoperative opioid use.

3.0 Background

With the increase in the aging population and the demand for better mobility and quality of life, total knee arthroplasty (TKA) is one of the most common elective surgical procedures in the US. By 2030, over 3 million people in the U.S. are expected to undergo TKA each year. Increasingly, TKAs are performed as same-day surgery to reduce cost of care. TKAs are associated with severe postoperative

pain, especially during physical therapy. Ineffective pain control slows full functional recovery while increasing cost of care. Despite improvements in prescription practices, opioids are still the gold standard for treating post-TKA pain. More than 95% and >10% use opioids within 1 week and at 1 month after TKA. In 80% of cases of uncontrolled pain, patients are prescribed opioids. Moreover, approximately 36% of TKA patients receive an opioid prescription beyond the recommended CDC dose. In elderly patients undergoing TKA, exposure to opioids increases risk for opioid use disorders (OUD) and adverse effects, including life-threatening opioid-induced respiratory depression, longer hospital stays, emergency room (ER) visits and overall costs. TKA is a leading cause for OUD after surgery further worsening socioeconomic burden. The COVID pandemic has worsened the opioid epidemic, leading to over 100,000 opioid overdose deaths. Recently, a special focus has been placed on opioid-sparing complementary approaches for postoperative pain control. FDA-cleared techniques including transcutaneous electrical nerve stimulation (TENS), implantable femoral nerve stimulator, and acupuncture are utilized to reduce opioid use for patients undergoing TKA. These techniques require training, and expertise, are short-lasting, and often are expensive. Femoral nerve blocks are effective but short-lasting and expensive. There remains an urgent and critical need for an easy-to-use, non-pharmacological pain relief alternative to opioids to cost-effectively facilitate full post-TKA recovery.

4.0 Study Endpoints

Primary Endpoints:

- Pain at rest assessed by a numerical rate scale (NRS 0=no pain and 10=worst pain) at week 1

Secondary and Exploratory Endpoints:

- Pain while walking 30 and 100 feet on days 0, 1, and on weeks 1, 2, and 6, respectively.
- Time to hospital discharge (length of hospital stay).
- Total opioid use in OME (mg) over 6 weeks from all data sources/PDMP.
- PONV, antiemetic use
- Prescribed opioid refills in the first 6 weeks based on the Prescription Drug Monitoring Program (PDMP)
- Functional recovery – range of motion
- Functional recovery – ability to walk 30 feet and 100 feet
- Patient satisfaction

Study Intervention/Investigational Agent:

The top layer of the NeuroCuple patch is made of medical-grade material that is flexible, durable, and latex-free. The nanocapacitors inside the patch detect and interact with the electrical signals from the body's nervous system through neuro capacitive coupling. The patch could absorb and redistribute negative charges at the local level that may be caused by discomfort and this redistribution has an anti-inflammatory and analgesic effect. Perhaps most importantly, this investigation could significantly decrease opioid requirement, postoperative pain, the length of hospital stay, the need for opioid prescription following discharge from the hospital, improve early functional recovery, and increase patient satisfaction.

Device Management and Storage:

The nCAP Patch will only be applied to qualifying subjects who consent to participate in the study. Only supporting staff trained in placement of the patch will apply the patch to study participants. The patches will be stored in a locked office that can only be accessed by research staff. The device will be labeled 'CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use.'

5.0 Procedures Involved

*Study Schedule of Events is attached to the end of this protocol document for reference.

Study Design:

This will be a double-blinded randomized (1:1) placebo-controlled clinical trial to determine the feasibility and effectiveness of a 2-week application of the NEUROCUPLE device for pain relief and reduction of opioid refills after TKA. We have a placebo device (sham device without the captor array layer) that looks exactly like the active device, allowing us to conduct a true placebo-controlled randomized study. The trial will include 120 participants over a 1-year period.

Study Intervention & Procedures Involved:

Written informed consent will be obtained prior to any of the research activities taking place. At the time of enrollment and consent, the subject will undergo the following screening with the study team.

Participant Screening:

Screening will be performed up to 7 days before surgery to determine inclusion and exclusion criteria. Patients who report a T-score ≥60 on any of the three PROMIS Short Form measures (i.e., sleep disturbance, anxiety, and depression), or have history of chronic pain, will be excluded.

Baseline Assessment:

Those who are deemed eligible to continue in the remaining of the research study activities from the initial screening will then complete the baseline assessment. The baseline assessment may take place at the time of subject consent and screening up to the morning of surgery. This assessment can be completed in-person with the study team or remotely via REDCap for convenience. The baseline assessment will consist of

collecting subject demographics, medical and medication history, as well as completing the (1.) Pain Catastrophizing Scale, (2.) SOAPP-R, and (3.) WOMAC. Lastly, a functionality assessment will be completed with the study team prior to surgery which consists of their ability to walk and measured as a binary (yes/no) response by the study team.

Randomization:

Subjects who complete the baseline assessment will then be randomized post-operatively to either receive the NEUROCUPLE or the Placebo (sham) patch. Subject's will not be made aware of which patch they are randomly assigned. Each randomized participant will be assigned a subject ID number, and this ID number will correspond to a treatment allocation based on a pre-designed randomization schema.

Intervention:

a) Standardized care (day 0): Both the placebo group and intervention group will receive approved ERAS multimodal standard of care (see below). Before transfer to the operating room, an ultrasound-guided adductor canal nerve block will be performed with 20 ml of 0.325% bupivacaine and a 22 g Tuohy needle. No opioid will be administered before surgery. TKA surgery will be performed under spinal anesthesia and sedation using propofol titrated to the needs of the patient. At the end of the surgery, 30 mL of 0.5% bupivacaine will be injected around the knee.

b) NEUROCUPLE or Placebo Application (after surgery on day 0 in the recovery room): After the TKA surgery, and after participants have been in the recovery room for 30 mins, they will have either a NEUROCUPLE or placebo device applied by a trained researcher. Measurement of circumference will be done under, on, and above the knee during placement of the patch. The NEUROCUPLE device will not be placed at the level of the wound on top of the knee. The NEUROCUPLE or placebo device will be placed around the lower thigh to allow free knee movement. The device will be contained within a sleeve and the two ends of the device will be secured using a Velcro band in the back of the lower thigh.

Measurement of circumference will be done above and below the knee at baseline, after placement of device/day of discharge, and at week 1,2, and 6.

Subjects will be asked to wear the patch daily for two weeks. They will be asked to wear the patch for at least 12-hours a day, with the exception to remove it when bathing or showering. They will be asked to stop wearing the patch at the week 2 timepoint.

c) Research Monitoring & Discharge:

Once the patch has been successfully placed by the research team, the subject will be monitored by the research team every 30-minutes (+/- 15-minutes) for up to 4-hours or until they are transferred from the recovery

room, which will include the Ramsay Sedation Scale, NRS pain scores, and collection of vital signs, medication usage, and oxygen saturation.

After recovery room transfer to the floor, subject's medical records will be monitored to collect medication usage, vital signs, and pain scores collected by the clinical team every 4-6 hours per SOC routine protocols. In addition, the research team will also collect the Ramsay Sedation Scale and NRS pain scores at these timepoints if absent. Lastly, the study team or clinical care team will complete a functionality assessment during their hospital stay and will be recorded as binary (yes/no) response.

UPMC has a standardized practice for post-TKA opioid prescribing at discharge; all surgeons comply with this standardized opioid prescription practice. The patient will be discharged from the hospital with an opioid prescription of 30 pills (oxycodone 5 mg every 4 h as needed; see ERAS Multimodal Standard of Care below) and instructed to call the surgeon's office for a refill (30 pills of oxycodone 5 mg) if needed. Approximately 30-40% of TKA patients are expected to be discharged within one day after the surgery.

At 24-hours (+/- 3-hours) OR at the time of discharge, the research team will provide knee circumference measuring instructions which includes providing several paper measurement devices for the subjects to obtain these measurements in the follow-ups. The subjects will be instructed to mark on their knee with a marker, above and below, the location of measurement. They will also receive their reloadable Vincent payment card, though these will not be loaded until weeks 2 and 6 respectively.

d) Follow-Up Assessments:

The research team will call the subject daily up to week 2 to determine if there are any issues or concerns with the patch, as well as to assess their pain levels.

The functionality assessment will be completed remotely via Telemedicine after the subject has been discharged and will occur on days 1-5 and week 1. Then on week 2 and week 6 with the research team.

In addition to the functionality assessments via Telemedicine, there will be emailed surveys via REDCap the subject will be asked to complete at 24-hours, 1-week, 2-weeks, and 6-weeks after hospital discharge. If participants do not have access to a computer or smart device, the study team will contact them via phone to complete these follow-up assessments. A research team member will contact participants on the day of follow-up and will verbally complete each assessment over the phone. Participants will continue to be contacted post-operatively to gather their responses to the surveys a maximum of three times. If the study team are unable to reach participants after three days, they will be removed from this study.

Study surveys will include questions regarding participants pain level and pain medication consumption following their surgery. These surveys will be sent to participants on 24-hours, 48-hours, 1-week, 2-weeks, and 6-weeks after their surgery. Participants prescription refills will also be monitored by the study team throughout their participation in this study. A full timeline and assessment details are provided in Table 1 Schedule of Assessments.

Lastly, subjects will be asked to complete the PROMIS Short Forms from the initial screening, the Pain Catastrophizing Scale, and WOMAC assessments at week 2 and week 6.

Data Collection:
Relevant medical and surgical history within last 90 days to be collected as part of pre-surgical standard of care from Electronic Medical Records (EMR). Medication history to include any history of opioid use and any other relevant medications within 90 days.

6.0 Data and Specimen Banking

We will ensure the quality of our data and protect its integrity in the following ways:

- Home address, phone numbers and subject names will be stored along with a unique personal identification number (PIN) on a HIPPA compliant website and data will only be stored with PIN. Questionnaires will be handled through a HIPAA compliant subject survey created on a HIPPA compliant platform (e.g., REDCap). Questionnaire data will be downloaded and stored with PIN only.
- Confidentiality Agreement and Consent forms will be signed electronically. The consent form will be recorded via REDCap and stored securely through on a HIPAA compliant folder. Three years following data acquisition, the key with subject identities will be deleted. De-identified data will be stored for an indefinite time.
- Stored data is identified only by subject PIN number. Consent and Confidentiality Agreement forms will be signed electronically and stored in HIPAA compliant websites. Address and phone numbers will be stored electronically on HIPAA compliant websites. Subject information may be provided to Federal and regulatory agencies as required by law.
- Paper-based records will be stored in locked filing cabinets, and all computer-based records that are not de-identified will be password protected. Each individual will receive a unique ID number thereby allowing handling of data on subjects without using individual names. Data maintained in computers will be accessible only to project staff.
- Shared data will be deidentified.

7.0 Sharing of Results with Subjects

nCAP Medical will follow NIH's policy, including the NIH Data Sharing Policy and Implementation Guidance on March 5th, 2023, as well as the HEAL Public Access and Data Sharing Policy. nCAP Medical will file for intellectual property protection on any new discoveries made as a result of this project. After appropriate intellectual property protection has been obtained, the Company will then disseminate the results through multiple mechanisms, including presentation at scientific and professional meetings and peer reviewed publications.

8.0 Study Timelines

- The duration of an individual subject's active participation will be 7 weeks (1 week prescreen + 6-week study)
- The duration anticipated to enroll all subjects is 1 year.
- The estimated date for the investigator to complete this study (complete primary analysis) is 06/30/2025.

9.0 Inclusion and Exclusion Criteria

Subjects will be approached at the time of their office visit after they are informed that they need TKA.

Inclusion Criteria:

1) >18 years of age
2) An Institutional Review Board (IRB) approved informed consent is signed and dated prior to any study-related activities
3) Scheduled for elective primary unilateral TKA
4) T-score < 60 on the PROMIS Anxiety measure

Exclusion Criteria:

1) Children (<18 yr.)
2) Pregnant women
3) Active alcoholism (defined as daily use of more than 1 liter of wine and /or 3 or more shots of hard liquor) or drug abuse (defined as daily use of illicit drugs)
4) Severe chronic pain condition that requires daily preoperative opioid dependence
5) T-score ≥ 60 on the PROMIS Anxiety measure
6) Other concomitant surgery being performed in addition to TKA
7) Patients undergoing bilateral TKA
8) Patients undergoing knee replacement revision
9) Patients with limited mobility (in a wheelchair or requiring a walker)

10) Patients who are not returning home after surgery

10.0 Vulnerable Populations

No children (<18 years of age), prisoners, or institutionalized individuals will be included in this study. Given the nature of the surgical procedure, pregnant women and women who may be pregnant will not be included.

11.0 Local Number of Subjects

This clinical trial will require 60 participants per group (120 in total) who undergo primary unilateral total knee replacement over 1 year. We plan to recruit 120 individuals, with 60 patients randomized in a 1:1 ratio of NEUROCUPLE™ (n=60) to placebo (n=60).

12.0 Recruitment Methods

1) Potential participants will be identified from the census of Dr. Klatt and Dr. O'Malley's Operating Room schedule up to one week prior to surgery.
2) Patients scheduled for surgery will be given information about this research during their pre-operative visit and they will be invited to participate in this research.
3) The investigators will ask permission to approach these patients to assess the patient's interest in participating in the study.
4) The clinical care team will introduce the study and request permission from the patient for the research team to speak with them.
5) If the subject agrees to be approached by a member of the research team, then the research team will approach the subject during the pre-operative visit.
6) If a potential subject is willing to sign consent, then a physician investigator will be available to review the risks and benefits of participation before obtaining informed consent.
7) All questions will be addressed, and it will be made clear that the patient may withdraw from the study at any time.
8) The Investigator physician will sign the informed consent with the patient prior to beginning of any study procedures.

Methods of Recruitment:

- Directly approaching potential subjects (in-person)
- Email/Listserv/Electronic Mailing List
- Flyers/Posters or Brochures

Compensation Offered to Participants:

Total possible compensation offered to participants is $250. Participants will receive $125 on each of the week 2 and week 6 follow-up assessments.

13.0 Withdrawal of Subjects

The subject will be informed many times during the consent process and throughout the study that if they do not like wearing the patch, the patch can be removed at any time, and

they will be discontinued from the study. Any non-compliance to the research activities will lead to them being involuntarily discontinued.

Subjects who remove the patch early (with no AE present) will be withdrawn due to non-compliance issues. Subjects who experience an AE related Human Research Protection 3500 Fifth Avenue, Suite 106 Pittsburgh, PA 15213 www.hrpo.pitt.eduto the patch will not be withdrawn, but the patch will be removed immediately, and data collection will ensue as normal.
If a participant withdraws from research, follow up will cease but data previously collected may still be used in analysis.

After withdrawing from the study, each subject's data will be kept for the required data retention period in a secure, locked facility, and will be destroyed after that period. Patients' data might be used for data analysis if deemed necessary/useful (e.g. reason of withdrawal).

If the collected patient data is no longer needed for the study and the required data retention (at least 7 years per University policy) period has expired then the paper records may be shredded and identifiers for computer-based records would be removed.

14.0 Risks to Subjects

Collection and Storage of PHI:

Investigators who will access the identifiable medical records already have normal clinical access to all necessary records, as granted by the privacy office for job-related needs. Thus, only HIPAA trained research staff will be handling this information and this information will be stored in a locked database protected by the UPMC firewall. Additionally, all data generated under this protocol will be monitored and maintained by the principal investigator. Any databases that contain identifiable information will be stored on a departmental drive on the UPMC network created for the principal investigator, and all data will be deidentified according to the HIPPA "safe harbor" guidelines prior to statistical analysis.

Only subject initials and an identification code (i.e., not names) will be recorded on forms submitted to the sponsor and IRB. The Investigator will keep a subject log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

NUEROCUPLE Patch:

Subjects may experience skin irritations or possible discomfort from the patch. If this occurs, the subject will be encouraged to discuss this with the study team. The study team will remind them that this study is completely voluntary, and they may remove the patch at any time. If the subject removes the patch, there is a possibility they will be involuntarily withdrawn from the study for non-

compliance, but they will be informed of this. Only study team members trained in proper placement of the nCAP Patch will be applying the patch.

Questionnaire Administration:

Subjects may experience discomfort from the personal nature of these questionnaires. They may also experience potential boredom due to the length of the questionnaires. Subjects may skip questions they feel are uncomfortable.

Functionality Assessment:

Subjects may experience discomfort from the expected walking distances following their surgery. Subjects will be reminded that they can stop if the discomfort becomes too great.

15.0 Potential Benefits to Subjects

This study will be conducted with patients undergoing TKA. Participants who are randomized to receive the treatment device (NEUROCUPLE) are expected to experience reduction in pain and in the need for opioids. All participants may derive satisfaction from engaging in research to advance a technology that reduces pain following surgery and reduces the risk of opioid dependence.

16.0 Data Management and Confidentiality

Power Analysis:

Pain score at rest at week 1:

Our preliminary data found that the mean (SD) of pain at rest scores (range 0-10) at week 1 was 2.4 (1.8) in NEUROCUPLE treatment group and 4.2 (3.1) in the standard-of-care group. This placebo-controlled clinical trial would require 33 per arm (66 participants total) to detect more than 2-point clinically meaningful reduction in pain at rest at week 1 with an 80% power at a 5% level of significance using a two-sided t-test allowing unequal variance.

Prescribed opioid refills in the first 6 weeks:

Our preliminary data show the use of the NEUROCUPLE device was associated with a 47% reduction in the number of patients requesting an opioid refill over the first 30 days in the treatment group (29%) vs. the standard-of-care group (55%). This placebo-controlled clinical trial would require 53 per arm (106 participants total) to detect a 47% reduction in the use of prescribed opioids in the first 6 weeks using a two-sided chi-square test.

Planned number of subjects:

To account for a 10% dropout rate, this clinical trial will require 59 participants per group (118 in total) who undergo primary unilateral TKA in one year. We plan to recruit 120 individuals randomized in a 1:1 ratio of NEUROCUPLE (n=60) to placebo (n=60) in one year, which is feasible based on our TKA volume and preliminary TKA study.

Data and Safety Monitoring:

We will include highly experienced clinical personnel to monitor the patients and ensure that no adverse effects are encountered. Specifically, this study involves two clinical

hospital sites: University of Pittsburgh Medical Center (UPMC) Shadyside and UPMC East. UPMC is an Acute Interventional Perioperative Pain Service (AIPPS) site, which offers 24-hour perioperative pain management for orthopedic, thoracic, and urologic patients. The specialists at these sites routinely participate in clinical research and will provide professional execution of clinical site tasks.

For the portion of the trial conducted remotely following patient discharge, we will monitor and report concerns using REDCap, a secure web application for building and managing online surveys and databases. Dr. Chelly and Dr. Sadhasivam, PIs of the proposal, will review REDCap and debrief with the clinical team.

We will conduct the monitoring through our functional recovery assessments on postoperative day 0, day 1, week 1, week 2, and week 6. As our team will monitor participant information regularly, we will be able to stop treatment at any point. Specifically, our plan to stop treatment is as follows: (1) at the request of the patient at any time, (2) if there is any complication of the surgery that impacts the safety of the patient, in the opinion of the PI or the surgeon, and (3) at the discretion of the PI or surgeon.

We will manage any adverse events listed above by reviewing severity, causality, and duration of adverse events on a regular and continuous basis though interaction with the subject during study visits, or at any time at the discretion of the subject. After discussion with the clinical team, Dr. Chelly will report adverse events and any unanticipated problems to the National Institute on Drug Abuse (NIDA) and the NIH Office of Biotechnology Activities. We will also report to any other parties as determined necessary by the NIH.

We will ensure the quality of our data and protect its integrity in the following ways:
a) Home address, phone numbers and subject names will be stored along with a unique personal identification number (PIN) on a HIPPA compliant website and data will only be stored with PIN. Questionnaires will be handled through a HIPAA compliant subject survey created on a HIPPA compliant platform (e.g., REDCap). Questionnaire data will be downloaded and stored with PIN only.

b) Confidentiality Agreement and Consent forms will be signed electronically. The consent form will be recorded via REDCap and stored securely through on a HIPAA compliant folder. Three years following data acquisition, the key with subject identities will be deleted. De-identified data will be stored for an indefinite time.

c) Stored data is identified only by subject PIN number. Consent and Confidentiality Agreement forms will be signed electronically and stored in HIPAA compliant websites. Address and phone numbers will be stored electronically on HIPAA compliant websites. Subject information may be provided to Federal and regulatory agencies as required by law.

Access to Study Records:

Subjects' records of being in the study will be kept private except when ordered by law. The following people will have access to study records:

- Phase 1 Unit Principal Investigator, sub investigators, and study staff
- Authorized representatives of the University of Pittsburgh Office of Research Protections may review identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.
- Authorized representatives of the study team, who are also part of the Department of Anesthesiology and the Acute Interventional Perioperative Pain Service, will review and/or obtain identifiable information (which may include identifiable medical information) related to participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.
- Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include identifiable medical information) related to participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).
- In unusual cases, the investigators may be required to release identifiable information (which may include identifiable medical information) related to participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.
- Authorized representatives of the U.S Food and Drug Administration (FDA) and other regulatory agencies may review and/or obtain identifiable information (which may include identifiable medical record information) related to participation in this research study for the purpose of monitoring the accuracy of the research data.

17.0 Provisions to Protect the Privacy Interests of Subjects

Research intervention will be conducted in a private room with the patient, collected information will be limited to that which is necessary for the goals of the research study, access to the patient's private information will be limited to those involved in the patient's medical care. Application of the nCAP Patch will be performed in the PACU behind a closed drape.

Subjects may experience discomfort from the personal nature of the questionnaires. They may also experience potential boredom due to the length of the questionnaires. Subjects may skip questions they feel are uncomfortable.

18.0 Economic Burden to Subjects

There will be no cost to the subjects for participating in this clinical trial.

19.0 Consent Process

Written informed consent will be obtained prior to any research procedures being performed. Subjects may be approached in-person or remotely, however, all informed consents will be collected electronically via the REDCap platform.

Patients may be provided information about the study in the respective preoperative clinic/surgical clinics or approached by the study team on the day of their scheduled surgery. If a subject is deemed eligible via inclusion/exclusion criteria, the clinical care team with introduce the study and request permission from the patient for the study team to speak with them. If the subject agrees to be approached, then a study team member will discuss the study with them at length and answer any questions they may have. If a potential subject is willing to sign consent, then a physician investigator will be available to review the consent, risks and benefits of participation, and obtain informed consent.

If the potential subject is identified prior to surgery either by the OR schedule, a clinic/surgical visit, or as a result from the research flyer, study team members will be able to review the study process, answer all questions the subjects may have, and review eligibility criteria with the potential subjects via telephone. The potential subject will then be given the option to sign e-consent remotely or to sign an electronic consent form the morning of their scheduled surgery. An investigator will be present in person for consent or remotely present via videoconferencing (using Microsoft Teams or Zoom).

Subjects will be provided a link via email for the sign the consent on REDCap. This link will include an electronic consent document and the ability to sign with a computer cursor, stylus, or their finger depending on the device the subject uses to access this link. The REDCap platform FDA 21 CFR Part 11 compliant.

If the subject does not receive the study material in the clinic, they will be approached the day of surgery. The subject will be approached as soon as they arrive (approximately 2-3 hours before their surgery) and will be given adequate time to consider the consent and ask questions. If the subject does not feel they have enough time to make a decision, they will not be enrolled in the trial.

The investigator anesthesiologist then will see the patient prior to surgery and discuss the consent form that may have been previously provided to the patient, including potential risks and benefits associated with the study.

On-Going Consent:

At each visit, the subjects will be asked if they have any questions and will be reminded about the goals and objectives of the study. The subjects will also be reminded that they can withdraw from the study at any time if they choose.

Ensure Subject's Understanding:

A member of the clinical care team will introduce the study to the potential subject, and only if the patient is interested in hearing more about the research, then a study team member will approach the subject to provide more information. To ensure that the subject has a full understanding and comprehension of what the study entails, the details of the informed consent, eligibility criteria and risks and benefits will be reviewed with the subject by a licensed physician investigator before signing consent on the morning of surgery. The subject will be encouraged to ask questions and all questions will be addressed, and a copy of the consent form that contains contact information for the investigator will be given to the subject.

20.0 Setting

Site of Research:

UPMC Shadyside is a hospital with an Acute Interventional Perioperative Pain Service (AIPPS). The anesthesiologists here routinely participate in clinical trials and various other types of clinical research, are well acclimated to conducting clinical research with respect to good clinical practice. There are sufficient resources of manpower and supplies to conduct the study.

21.0 Statistical Analysis Plan

Analysis of Endpoints: Wilcoxon two sample tests were used to compare continuous endpoints between the active and sham groups, and Chi-square tests were used to compare categorical endpoints between two arms. Missing data were handled using the last observation carried forward (LOCF) approach. Standardized Mean Differences (SMD) were calculated as the difference in group means divided by the pooled standard deviation of the endpoint between treatment groups. SMD ≥ 0.2 indicates that the two groups are different. Total PONV and rescue antiemetic use divided by number of participants in each group were analyzed. Incidence Rate Ratios (IRRs) were estimated using negative binomial regression models.

Longitudinal Analysis: To examine the treatment effect of the NBD across time and account for the time effect of days (from day zero to week one) and correlation of repeated measures, generalized linear mixed models (GLMM) were performed for longitudinal outcomes, including pain at rest and opioid consumption.

All the analyses were performed using an intention-to-treat approach. Statistical significance was set at a P-value < 0.05. SAS 9.4 (SAS Institute, Cary NC, USA) and R (R Foundation for Statistical Computing) were used for statistical analyses.

Table 1- Study Assessments and Timeline	Screening	Baseline	PACU	DAS	Day 0/Discharge Day	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Week 1	Week 2	Week 6
-Visit Window	-7 to 0 Day	-7 to 0 Day	0 Days	0 Days	0 Days	Days 1-2						± 3 Days	± 3 Days	± 3 Days
-Visit Type	S	S or H	H	H	C	T	T	T	T	T		T	C	C
-PROMIS® Short Forms Anxiety, Sleep, and Depression	P												P	P
-Pain catastrophizing scale	P												P	P
-Driving Questionnaire													P	P
-Demographics and Medical History		P												
-Opioid and non-opioid analgesic consumption	C	C	C	C	C	P	P	P	P	P	P	P	P	P
-Potential risk for opioid misuse (SOAPP-R)		P												P
-Opioid prescription refills (PDMP)	C											C	C	C
-Ability to climb 5 steps (yes /no)			C/P	C/P	P							P	P	P
-NRS Pain Intensity at Rest/Movement • **Least/ Worst/ Average**		P	C/P	C/P	P	P	P	P	P	P	P	P	P	P
-NRS with Movement • **Ability 30ft/ Ability 100ft/ NRS Intensity after walking**		P		C/P	P	P						P	P	P
-WOMAC index		P											P	P
-Lower Extremity Functional Scale		P											P	P
-Ramsay sedation scale			C	C	C									
-Range of motion (ROM)						P/CT/PT						P/CT/PT	C	P/CT/PT
Above knee circumference of both knees		C			C	C						P	C	C
-Vitals					AO*									
-Time of discharge					C									
-Adverse events, protocol deviations					C	C						C	C	C
-Patient Satisfaction - 3 Surveys for Care, Device, Pain, 1 survey for perception of Device													P (4)	P (2-Care/ Pain)
Device Compliance						P	P	P	P	P	P	C	C	

*: Either; H: Hospital; S: Surgeon Office; PT: Physical Therapist; T: Telemedicine; A: Ambulatory; O: Observational; P: Patient self-report; C: Coordinator; NRS: Numerical Rating Scale; PDMP: Prescription Monitoring Program; SOAPP-R: Screener and Opioid Assessment for Patients with Pain-Revised

Table 1: Study Assessments and Timeline