Official Title: Percutaneous Auricular Neuromodulation for Postoperative Analgesia: A Randomized, Participant- and Observer-Masked, Sham-Controlled Pilot Study

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UCSD Human Research Protections Program

New Biomedical Application
RESEARCH PLAN

Instructions for completing the Research Plan are available on the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 9/30/2013

1. PROJECT TITLE

Percutaneous Auricular Neuromodulation for Postoperative Analgesia: A Randomized, Participant- and Observer-Masked, Sham-Controlled Pilot Study

2. PRINCIPAL INVESTIGATOR

Brian Ilfeld, MD, MS

3. FACILITIES

UCSD health system: Thornton Hospital, Jacobs Medical Center, Hillcrest Medical Center, KOP

4. ESTIMATED DURATION OF THE STUDY

Three years (1 month preparation, 24 months enrollment, 11 months publication prior to closure)

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

The moderate-to-severe pain many patients experience following surgery is often treated with opioids, which are associated with side effects such as nausea/vomiting, sedation, and respiratory depression (and a risk of abuse, dependence, and diversion). Potent site-specific analgesia with fewer side effects may be provided with peripheral nerve blocks. However, these too have limitations such as a duration of action measured in hours, while the pain from surgery is usually measured in days or weeks. Peripheral nerve stimulation or "neuromodulation" is an alternative method of pain control involving the introduction of electrical current to stimulate various nerves that do not carry pain sensations, but which then decreases communication between pain fibers and the spinal cord and/or brain. Placing small electrodes specifically in the area of the ear is called "auricular neuromodulation" and is theorized to function by stimulating various cranial and peripheral nerves that influence a part of the brain called the "limbic system" which is involved with many aspects of behavior including responses to stress. A device that delivers auricular neuromodulation, the "Bridge" system, is approved by the US FDA for use to reduce symptoms associated with opioid withdrawal for up to 5 days. However, one prospective and two published retrospective studies suggest that it may provide postoperative analgesia as well. The device itself is relatively simple to apply; has few contraindications, side effects, or adverse events; and has no potential for dependence, abuse, or diversion. Therefore, it has the potential to concurrently improve analgesia and decrease or even negate opioid requirements following surgery, only without the limitations of opioids and peripheral nerve blocks. The purpose of this pilot study is to explore the possibility of treating postoperative pain with percutaneous auricular neuromodulation, optimize the study protocol, and estimate the treatment effect in preparation for developing a subsequent definitive clinical trial.

6. SPECIFIC AIMS

The proposed study will be a randomized, participant- and observer-masked, sham-controlled, parallel-arm, human participants pilot study with two primary aims:

Specific Aim 1: To determine the **feasibility** and **optimize** the protocol for a subsequent clinical trial that will compare the addition of percutaneous auricular neuromodulation to usual and customary analgesia following moderate-to-severely painful surgical procedures.

Specific Aim 2: To ***estimate*** the **treatment effect** of adding percutaneous auricular neuromodulation to usual and customary analgesia on pain and opioid consumption following various surgical procedures. This will provide an idea of the optimal surgical procedures amenable to this analgesic technique and allow determination of the required **sample size** of a subsequent definitive clinical trial.

Hypothesis 1: *Auricular neuromodulation decreases **pain** in the 5 days following moderate-to-severely painful surgical procedures currently treated with a single-injection peripheral nerve block.*

Hypothesis 2: *Auricular neuromodulation decreases **opioid use** in the 5 days following moderate-to-severely painful surgical procedures currently treated with a single-injection peripheral nerve block.*

7. BACKGROUND AND SIGNIFICANCE

The moderate-to-severe pain many patients experience following surgery is often treated with opioids, which are associated with side effects such as nausea/vomiting, sedation, and respiratory depression (and a risk of abuse, dependence, and diversion). Potent site-specific analgesia with fewer side effects may be provided with peripheral nerve blocks. However, these too have limitations such as requiring an anesthesiologist for administration, a duration of action measured in hours, and rendering the target area/limb insensate.

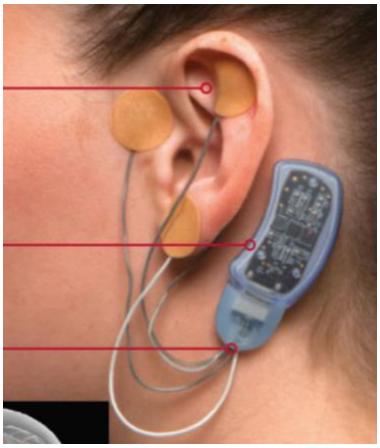
An analgesic alternative with few associated limitations is **neuromodulation**. Below the foramen magnum, this technique is based on Melzack and Wall's "gate control theory" in which electric current stimulates large-diameter afferent peripheral nerves that subsequently interrupt communication (the "gate") from small-diameter pain fibers to the central nervous system at the level of the spinal cord.[2] In contrast, the mechanism of action for nerves above the foramen magnum is multifactorial and less well elucidated, although indirect "gating" has been hypothesized.[1] Functional MRI studies suggest that stimulation of one part of the ear—the "cymba conchae" just posterior to the crus of the helix—results in activation of the primary somatosensory cortex, amygdala, fornix, thalamus and insula; and deactivation of the hippocampus and hypothalamus.[2] However, the peri-auricular innervation is very complex with contributions from cranial nerves V (auriculotemporal branch of the mandibular nerve), VII (posterior auricular branch of the facial nerve), IX (glossopharyngeal nerve) and X (auricular branch of the vagus nerve) as well as the occipital and great auricular nerves from the 2nd and 3rd cervical levels.[3] Stimulation of different anatomic locations results in differing effects, although all sites are believed to influence the limbic system which is involved with many aspects of behavior, including responses to stress.[3]

Additional possible mechanisms for auricular neuromodulation are multifactorial, complex, and only partially understood.[1] They include the modulation of serotonergic, noradrenergic, and endorphinergic pathways with associated release of serotonin, norepinephrine, and endogenous opioids such as beta-endorphins.[4] Vagal stimulation further chemically modulates nociceptive (pain) processing, anxiety, and depression.[5,6] Many neurotransmitters are influenced, such as increasing gamma-aminobutyric acid (GABA) which can lead to anxiolysis.[7] Complex neuropathways exist from the auricle to the brainstem, higher brain structures, the spinal cord, and finally to multiple organs *via* spinal nerves.[1] Given the large number of effects auricular stimulation produces, it is unsurprising that it has multiple therapeutic uses, including treating neurological (e.g. epilepsy), inflammatory, and

cardiovascular disorders; metabolic syndromes; psychiatric symptoms and disorders (e.g., anxiety, depression, autism);[8] as well as multiple pain conditions.[7] The auricular neuromodulation device proposed in the current study—the **NSS-2 Bridge**—is FDA cleared to reduce symptoms associated with opioid withdrawal.[9-11] Three small uncontrolled retrospective and prospective studies suggest that this device may also provide analgesia and/or decreases opioid use following surgery.[12-14] The proposed mechanisms for these findings are, unsurprisingly, multifactorial.

Anti-nociceptive mechanisms. As noted previously, stimulation of the vagus nerve chemically modulates nociceptive (pain) processing, anxiety, and depression.[5,6] In addition, vagus stimulation results in anti-inflammatory effects which is hypothesized to counteract pain hypersensitivity.[1] Unlike in the peripheral nervous system below the foramen magnum, A-beta afferent fibers of the auricle and pain-conducting A-delta and C nerves throughout the body do not originate in the same location. Therefore, a direct "gating" mechanism is not possible with stimulation of cranial nerves. However, an indirect gating mechanism is theorized since afferent cranial nerve fibers end in the lower medulla (specifically the nucleus of the solitary tract);[15,16] which itself interacts with other areas of the brainstem involved in pain processing.[17] Additionally, a more traditional spinal cord gating mechanism might occur with auricular stimulation of the occipital and great auricular nerves, both originating from cervical roots 2 and 3.[18] Both of these indirect and direct gating mechanisms may function by producing descending inhibitory impulses and stimulating encephalin-containing interneurons which impede ascending nociceptive signals within the spinal cord.[19-21] It is probable that traditional auricular acupuncture shares these mechanisms;[22] but since electrical stimulation of the auricle has demonstrated a positive correlation between current intensity and analgesia,[23-25] it is possible that electrical auricular stimulation will provide superior analgesia to traditional acupuncture, as has been previously reported.[26] Importantly, multiple studies demonstrate that neurologic effects of auricular stimulation outlast the stimulation itself, suggesting a mechanism for the prolonged analgesia reported in clinical use.[26,27]

Indeed, auricular neuromodulation has been reported to provide analgesia and/or decrease supplemental analgesic requirements for a plethora of indications, including chronic pain states[26,28-30] and acute migraine[31] and intra-procedure pain during *in vitro* fertilization,[32] intraoperative anesthetic requirements,[33] and postoperative pain following anterior cruciate ligament reconstruction,[34] laparoscopic nephrectomy,[35] tonsillectomy,[36] and hysterectomy.[37] In contrast, auricular neuromodulation failed to provide benefits following gynecological surgery,[38] and molar tooth extraction.[21] Several prospective and retrospective series involving the NSS-2 Bridge system suggest possible analgesic improvements following gastric bypass,[12] kidney donor surgery,[13] and Cesarean delivery.[14]



The <u>NSS-2 Bridge</u> (Masimo, Irvine, CA) is a small, single-use, drug-free, non-surgical, battery-powered stimulator that is adhered directly to the skin behind the ear [figure]. Three electrodes and one ground are introduced through the skin with tiny integrated solid-bore needles which do not require pretreatment with intra-dermal anesthesia (e.g., lidocaine skin wheal). The device is FDA cleared to reduce symptoms associated with opioid withdrawal and functions for up to 5 days.[9-11] Opioid withdrawal symptoms include anxiety, insomnia, muscle aches, nausea, and vomiting, ***all of which are frequent following surgery***.[39] There are only three relative contraindications to use: concurrent use of another neuromodulation device (e.g., cardiac

pacemaker), bleeding disorder or anticoagulation, and skin abnormality at the treatment site such as psoriasis vulgaris. Treatment-emergent adverse events (19,312 skin punctures in total) included minor bleeding at the skin (0.91%), dermatitis (0.91%), and significant pain during placement (0.17%).[11] A **zero** incidence of syncope, infections, and side effects was observed.[11] The FDA determined the NSS-Bridge to have a Class II risk designation, a class that includes surgical gloves and sphygmomanometers (blood pressure cuffs). ***With its ease of insertion, low risk of adverse events, lack of side effects, prolonged duration of action, and simple removal, auricular neuromodulation has the very real possibility of replacing opioid analgesics—the standard of care for the past 100 years—that would completely revolutionize postoperative analgesia, as we know it.***

Device risk catagorization. Treatment of postoperative pain is not currently an FDA cleared indication. However, the investigators believe the Bridge to be a nonsignificant risk device regardless of the indication (e.g., opioid withdrawal symptoms, analgesia, antiemetic). Per the FDA, a ***significant*** risk device is one that "presents a potential for serious risk to the health, safety, or welfare of a subject."

Of the risks of the Bridge device, "**minor bleeding**" at the skin (0.91%) included as little as a single drop of blood; but regardless, any bleeding is less serious than most childhood scratches and is treated with simple pressure. There is no risk of hemorrhage, and we do not believe this risk rises to the level of a "serious risk to the health, safety, or welfare" of a patient. Similarly, the risk of **dermatitis** (0.91%) is due to the adhesive on the bandages used to hold in the leads and the unit behind the ear—it is a similar adhesive to that used for "Band-Aids". If any dermatitis occurs, the unit can simply be removed, and the dermatitis resolves without treatment. Therefore, we do not believe this rises to the level of a "serious risk to the health, safety, or welfare" of a patient. The 0.17% incidence of "**significant pain** during placement" involved patients in opioid-withdrawal having the leads inserted with no analgesic added. Patients in opioid-withdrawal experience hyperalgesia and yet the incidence was only 0.17%. Our postsurgical patients will have been provided opioids as part of their surgical care to provide analgesia preoperatively for regional peripheral nerve block administration, intraoperative and postoperative pain, and to decrease sympathetic response during intubation for patients having a general anesthetic. We therefore anticipate the risk of severe pain to be far lower than 0.17%—most-likely zero. The standard of care pain medication for surgery is expected to provide sufficient analgesia for placement of the device.

Per the FDA, ***non-***significant risk devices "include most daily-wear contact lenses and lens solutions, ultrasonic dental scalers, and ***Foley catheters*** [emphasis added]." There is no know incidence of **infection** with the Bridge device. In contrast, a Foley catheter—determined to be a nonsignificant risk device by the FDA—has an overall infection incidence of 10.5% (15.5% in women); and a urinary tract infection can develop into pyelonephritis with significant morbidity and mortality [Saint et al. JAMA Intern Med. 2018;178(8):1078-85]. So, if the FDA has designated the Foley catheter with its 10.5% incidence of infection as a nonsignificant risk device, we believe that the Bridge with no known infections in over 19,000 lead insertions to also be a nonsignificant risk device.

Therefore, we do not believe that an IDE is required for the currently-described investigation. Consequently, we propose a randomized, participant- and observer-masked, sham-controlled, parallel-arm clinical pilot study to demonstrate feasibility and optimize the protocol as well as

estimate the treatment effect to allow the design and power of subsequent definitive multicenter, randomized, controlled clinical trials. ***The primary hypotheses are that percutaneous peripheral nerve stimulation decreases pain and opioid use in the 5 days following moderate-to-severely painful surgical procedures currently treated with a single-injection peripheral nerve block.***

8. PROGRESS REPORT

N/A

9. RESEARCH DESIGN AND METHODS

This will be a single-center (UCSD), randomized, participant- and observer-masked, sham-controlled, parallel-arm human participants pilot study.

Enrollment. Participants will be consenting adults undergoing various surgical procedures usually resulting in moderate-to-severe postoperative pain and treated with single-injection peripheral nerve blocks. Study inclusion will be proposed to eligible patients prior to surgery. If a patient desires study participation, written, informed consent will be obtained using a current UCSD IRB-approved ICF. The study population of interest includes women and men of all races, ethnicity, sexual identity, and socioeconomic status. Inclusion and exclusion criteria are listed in section #10 below.

Preoperative Procedures. Following written, informed consent, we will record baseline anthropometric information (age, sex, height, weight, current pain level). Participants will have their single-injection peripheral nerve block administered using ropivacaine 0.5% with epinephrine (standard at UCSD) prior to undergoing their surgical procedure *per standard of care*. A "successful" regional block will be defined as sensory- and motor-block onset in all expected nerve distributions within the 30 minutes following the local anesthetic injection. Participants with a successful regional block and undergo the anticipated surgical procedure will be randomized and continue within the study.

Treatment Group Assignment. Each participant will be randomized to one of two treatment groups: Active *(Experimental)* or Sham treatment. There are sham devices produced that are identical to active devices, only they do not deliver electrical current. Randomization will be stratified by surgical procedure, in block sizes of 2. The computer-generated randomization list will be created by the University of California San Diego Investigational Drug Service in a 1:1 treatment group ratio using opaque envelopes opened only after successful peripheral nerve block administration and the participant underwent the anticipated surgical procedure. The active and sham stimulators are indistinguishable in appearance, and therefore investigators, participants, and all clinical staff other than the individual who opens the randomization envelope and chooses a sham or active device will be masked to treatment group assignment for the duration of the data collection period.

Study intervention. The NSS-2 Bridge device will be affixed to the ear and activated prior to discharge from the recovery room *(Experimental)*. There is currently no consensus regarding the placement on the ipsilateral or contralateral ear relative to the surgical procedure (if sided). Therefore, we will apply the device to the side that the participant sleeps on least, to optimize comfort in bed and sleep.

Postoperative course. In addition to the experimental device and single-injection peripheral nerve block, participants will receive standard-of-care oral and intravenous postoperative analgesics which can include acetaminophen, ibuprofen, ketorolac, and opioids (this is surgeon- and patient-dependent). *Therefore, <u>all</u> patients of this study—regardless of the treatment arm they are randomized to—will continue to receive current usual and customary analgesia: all will receive the same combination of acetaminophen, ibuprofen, ketorolac, opioids, and a single-injection peripheral nerve block as they would regardless of study participation.* Prior to discharge, participants and their caretakers will be provided with verbal instructions regarding the care of the stimulator, and the telephone and pager numbers of an investigator available at all times during the first 5 days of treatment. The instructions for the stimulator are few: (1) you can shower, but use a shower cap to cover the stimulator; (2) there are no controls so there is nothing that needs to be adjusted; (3) the device will run out of power after 5 days; (4) we will call you every day to answer any questions you might have and describe how to remove the device as that time approaches.

Participants will be discharged when ready, as determined by standard criteria by the masked surgical service. Participants will be discharged home with their NSS-2 Bridge *in situ* and a prescription for immediate-release oral opioid, preferably oxycodone 5 mg tablets, taken for breakthrough pain. Participants will be contacted by telephone for end point collection beginning on postoperative day 1. The NSS-2 Bridge devices will be removed by patients or their caretakers at home on postoperative day 5. Similar to perineural catheters,[135] this procedure encompasses simply removing the small dressings (the electrodes remain adhered to the dressings and therefore do not require a separate extraction step), removing the stimulator from behind the ear with simple traction, and discarding all components (these are disposable, single-use devices).

At the conclusion of the study, participants will be informed of the main results in lay-person language by either email or the U.S. Postal Service.

Outcome measurements (end points). We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain-related clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement. All data collection will be through standard UCSD nursing/therapy EPIC notes and patient interviews in-person during hospitalization or *via* a telephone call. Postoperatively, surgical endpoints will be recorded such as surgical duration and tourniquet duration (if applicable). All pain scores will be measured using the Numeric Rating Scale (0: no pain, 10: worst imaginable pain).

Primary end points: This is an exploratory pilot study to assist in planning a subsequent definitive trial and we therefore have no data analysis plan. The two primary outcomes will be (1) the mean of the "average" pain recorded on postoperative days 1-5 measured with the Numeric Rating Scale ("average" pain is included in the Brief Pain Inventory pain domain); and (2) the cumulative opioids consumed from recovery room discharge until postoperative day 5, as measured in oral oxycodone equivalents.

Summary of post-enrollment assessments (color added for clarity)

Time Point:	Postoperative **Days**							
	1	2	3	4	5	6	7	8
Opioid consumption	•	•	•	•	•	•	•	•
Average Pain [NRS]	•	•	•	•	•	•	•	•
Worst Pain [NRS]	•	•	•	•	•	•	•	•
Brief Pain Inventory, Short Form		•		•		•		•
Sleep disturbances (#) previous night	•	•	•	•	•	•	•	•
Masking Assessment	•							

10. HUMAN PARTICIPANTS

We will recruit a convenience sample with a maximum of **150 participants**. Selection for inclusion will not be based on race, ethnicity, sexual identity, or socioeconomic status. There will be no participants from vulnerable populations, such as pregnant women, children, or prisoners.

Inclusion criteria: (1) undergoing one of the surgical procedures listed below as a primary procedure (not revision); (2) analgesic plan includes a single-injection peripheral nerve block with a long-acting local anesthetic [may be waived for hip arthroplasty]; and (3) age 18 years or older.

a. septoplasty [infraorbital nerve block]
b. laparoscopic cholecystectomy [transversus abdominis nerve block]
c. laparoscopic sleeve gastrectomy [transversus abdominis nerve block]
d. non-mastectomy breast surgery [paravertebral nerve block]
e. percutaneous nephrolithotomy [erector spinae plane nerve block]
f. inguinal hernia repair [transversus abdominis nerve block]
g. knee arthroplasty [adductor canal nerve block]
h. hip arthroplasty [pericapsular nerve group block]
i. shoulder acromioclavicular joint repair, labral repair, subacromial decompression, or Bankart repair (without rotator cuff repair) [interscalene nerve block]
j. orthopedic hardware removal anticipated to be at least moderately painful postoperatively [various peripheral nerve blocks]

Exclusion criteria: (1) concurrent use of another electric stimulator (e.g., cardiac pacemaker); (2) bleeding disorder; (3) anticoagulation; (4) skin abnormality at the treatment site; (5) psoriasis vulgaris; (5) morbid obesity as defined by a body mass index > 40 (BMI=weight in kg / [height in meters]^2); (6) history of opioid abuse; (7) inability to communicate with the investigators or hospital staff; (8) pregnancy; (9) bilateral or multi-stage surgical procedures; (10) incarceration; (11) chronic opioid or tramadol use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks); and (12) neuro-muscular deficit of the surgical area/limb.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

The investigators will need to know in advance which patients would like to participate in order to have an investigator and research coordinator present on the day of surgery. The investigators therefore need to contact potential participants prior to their pre-surgery visit and request a waiver of consent for recruitment purposes. We will scan the upcoming surgery schedule (which we have access to being anesthesiologists—we use this schedule daily for medical purposes), identify patients having the types of surgical procedures specified for this study, look in their electronic records to determine eligibility, and if eligible either call the potential participants ourselves or provide the name and contact information to a research coordinator to contact the potential participants.

1. These procedures are minimal risk to the potential participants as we are anesthesiologists who will be viewing these records even without study participation in preparation for surgery and postoperative analgesia planning. There is no information that an anesthesiologist would not view regardless of the existence of the study.

2. A waiver of consent would not adversely affect the rights and welfare of the potential participants as we are anesthesiologists who will be viewing these records even without study participation in preparation for surgery and postoperative analgesia planning. There is no information that an anesthesiologist would not view regardless of the existence of the study.

3. This clinical trial could not be practicably carried out without the waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or, they are seen just 1-2 days prior to their date of surgery. The investigators will need to know in advance which patients would like to participate in order to have an investigator and research coordinator present on the day of surgery. In addition, we need to bring participants to the surgical center 15 minutes earlier than regularly-scheduled in order to record baseline measurements.

4. After participants are contacted, if they would like to participate they will receive written, informed consent using an IRB-approved informed consent form.

These procedures would also include access to PHI, so we request a partial waiver of HIPAA authorization to be granted:

1. Identifiers will include the potential participant's date of surgery, surgeon, name, phone number, and email address (to send ICF if patient is interested in participation). This information will be recorded in hard-copy format and destroyed using a paper shredder (or in the locked UCSD PHI disposal stations) following contact with the patient. If the patient does not participate, then there will be no record of PHI whatsoever. If the patient does participate, then PHI will be protected as described in #16 below.

2. This clinical trial could not be practicably carried out without the waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or, they are seen just 1-2 days prior to their date of surgery. The investigators will need to know in advance which patients would like to participate in order to have an investigator and research coordinator present on the day of surgery. In addition, we need to bring participants to the surgical center 15 minutes earlier than regularly-scheduled in order to record baseline measurements.

3. The privacy risk to individuals whose PHI will be used is minimal since, as anesthesiologists at UCSD caring for ambulatory surgery patients, we use the surgery schedule daily in the normal course of our work caring for patients; and we will not record any PHI other than date of surgery, surgeon, name, contact phone numbers, and email address—and, these will be destroyed following use. The anticipated benefit to participants is a chance of improving their postoperative pain control if they are randomized to active stimulation.

4. PHI that will be used includes date of surgery, surgeon, name, contact phone numbers, email address, basic anthropometric data such as height and weight, past medical and surgical history, and the surgical schedule itself. Only coinvestigators will access this PHI, and the only people they might share it with are research coordinators actively participating in this research who understand PHI procedures and to appropriately destroy the hard copy of date/surgeon/name/contact numbers/email address after use.

Patients meeting inclusion and exclusion criteria will be presented with the study, and prospective study participants desiring additional information will be required to give permission for a research coordinator to contact them to adhere to HIPAA requirements. The study protocol will be reviewed with interested prospective participants in detail; and for participants desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or interventions. The method of documenting consent will be using written informed consent forms approved by the local Institutional Review Board.

12. INFORMED CONSENT

Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled to arrive the day of surgery 15 minutes earlier than normal to allow for written informed consent and baseline information collection. Written informed consent will be attained prior to any measurements or procedures prior to surgery. When participants present for surgery, research coordinators will provide and attain written informed consent. This will occur in private patient care areas, so that participants may feel comfortable asking questions of the research coordinator.

We do not foresee any issues relevant to the mental capacity of the potential human participants. Written, informed consent will be attained prior to any study procedures or measurements; and participants will not receive procedure-related sedation until following the written, informed consent process is completed. Participants will be provided privacy and time for decision making both in the study description/explanation telephone call to an investigator or research coordinator, as described above; and also the morning of the initial treatment using a private patient care area to again review the study, informed consent form, and answer any remaining questions. As noted previously, participants may speak with an investigator by telephone from initial contact through the morning of

treatment; and will have access during and following the treatment(s) with cellular phone and pager numbers provided upon discharge.

This study protocol has follow-up data-collection telephone calls a maximum of 8 days following the initial study treatment, so repeated informed consent following the initial consent is unnecessary, as opposed to multi-year, longer-term clinical trials. Surrogate consent will not be accepted; therefore, if human participants cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative is unacceptable for study enrollment.

Following informed consent and the signing of the UCSD IRB-approved ICF and HIPAA documents, these documents will be copied, and the copy placed in the patient's medical record. The participant will be provided a copy along with the Participants' Bill of Rights.

13. ALTERNATIVES TO STUDY PARTICIPATION

Patients can decline enrollment. If they do so, they will still receive the standard-of-care postoperative analgesia.

14. POTENTIAL RISKS

Potential risks include minor bleeding at the skin (0.9%), dermatitis (0.9%), and significant pain during placement (less than 0.1%). In addition, there is the risk of infection and loss of confidentiality. The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in locked medical offices and the locked Investigational Drug Service's files. Any digitized records containing personal health information will be stored as password-protected and encrypted files.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

The procedural risks involved with the intervention will be managed according to the complication:

- minor bleeding at the skin (0.9%): pressure would be held until bleeding ceased
- dermatitis (0.9%): the device would be removed
- significant pain during placement (far less than 0.17%): The participant could opt to not have it placed and be removed from study participation
- infection (theoretical: none reported to date): We would remove the device and possibly prescribe oral antibiotics, depending on the severity of the infection.

During use, placement of the device may restrict some normal activities such as bathing and brushing/arranging hair. While the device is water resistant, participants will be verbally instructed to avoid submerging it and should use a shower cap when showering. The small wires could get pulled out accidentally, so participants will need to brush/arrange hair with care. And, while we will place the device on whichever ear participants prefer, it may be less comfortable sleeping on the side with the device if a participant sleeps on both sides during the night.

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

We request a partial waiver of HIPAA authorization to be granted as explained above in section #11. Identifiers will include the potential participant's date of surgery, surgeon, name, phone number, and email address (to send ICF if patient is interested in participation). This information will be recorded in hard-copy format and destroyed using a paper shredder (or in the locked UCSD PHI disposal stations) following contact with the patient. If the patient does not participate, then there will be no

record of PHI whatsoever. If the patient does participate, then PHI will be protected as described below:

The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in a locked medical office. Only the investigators will have access to the records. Any electronic records with patient identifiers will be password protected according to UCSD IT recommendations and policies. No patient identifiers will be used in reporting data from the study. Every effort will be made to assure protection of patient privacy.

This study will require access to the medical record of patients who have consented to participate as participants. The privacy of these patients will be protected in the manner described below:

1. Specific consent will be obtained from each patient to permit examination of his or her medical record.
2. Information obtained during the study will be de-identified with study specific identifiers that do not permit recognition of any participants' personal information.
3. All information gathered will be stored in a locked cabinet which is inside a locked room which will be accessible only to registered study investigators.
4. Any data gathered stored on portable electronic media (e.g. flash drives) will be stored in this cabinet when not in use.
5. Any digitized records will be stored in encrypted files on password-protected computers.
6. No photographs will be taken.

17. POTENTIAL BENEFITS

Participants may or may not receive these benefits: decreased pain, opioid consumption, sleep disturbances, and pain-induced physical and emotional dysfunction.

Possible benefits to others: Future patients may benefit if it is determined that auricular neuromodulation decreases the incidence and severity of pain following moderately painful surgeries, as well as exposure to opioids during the postoperative period. Finding an effective non-opioid analgesic would be a tremendous step forward in helping future patients.

18. RISK/BENEFIT RATIO

While there are risks involved in the placement and use of the NSS-2 Bridge devices, they are relatively rare and not catastrophic when they do occur. With its ease of insertion, low risk of adverse events, lack of side effects, prolonged duration of action, and simple removal, auricular neuromodulation has the very real possibility of replacing opioid analgesics—the standard of care for the past 100 years—that would completely revolutionize postoperative analgesia, as we know it.

19. EXPENSE TO PARTICIPANT

None

20. COMPENSATION FOR PARTICIPATION

None

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator and Co-investigators are board-certified anesthesiologists with fellowship training in regional anesthesia and acute pain who place peripheral nerve blocks and manage acute

pain on a regular basis. All hold a license to practice medicine in California, have medical privileges at the UC Medical Centers, and will be responsible for the overall management of this study.

Investigators: Brian Ilfeld, MD, MS; John Finneran, MD; Engy Said, MD; Rodney Gabriel, MD, MS; and Matthew Swisher, MD, MS.

Baharin Abdullah is the current Program Manager of the Division of Regional Anesthesia and Acute Pain Medicine, and will therefore be performing regulatory work, consenting participants, and collecting data.

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24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable

26. IMPACT ON STAFF

There will be no appreciable impact on nursing staff as the study intervention will take fewer than 5 minutes while the patient is in the recovery room, and will not add to recovery room stay duration; and will not require any attention from the recovery room nursing staff.

27. CONFLICT OF INTEREST

None

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable

29. OTHER APPROVALS/REGULATED MATERIALS

Not applicable

30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT

Not applicable: surrogate consent will not be accepted.