Official Title: Cryoanalgesia to Prevent Acute and Chronic Pain Following Surgery: A Randomized, Double-Masked, Sham-Controlled 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.

1. PROJECT TITLE

Cryoanalgesia to Prevent Acute and Chronic Pain following Surgery: A Randomized, Double-Masked, Sham-Controlled Study

2. PRINCIPAL INVESTIGATOR

Brian M. Ilfeld, MD, MS

3. FACILITIES

UCSD hospitals and the UCSD CTRI

4. ESTIMATED DURATION OF THE STUDY

Five years (including follow-up and analysis)

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

Knee and shoulder arthroplasty, rotator cuff repair, video-assisted thoracoscopic surgery, and skin grafting for burn repair all result in both acute, and frequently persistent post-surgical pain. In addition, following mastectomy or limb amputation, pain perceived in the part of the body that no longer exists often develops, called "phantom" breast or limb pain, respectively. The exact reason that chonic and phantom pain occur is unclear, but when a nerve is cut changes occur in the brain and spinal cord that are associated with persistent pain. The negative feedback-loop between the injured body part and the brain can be stopped by putting local anesthetic—called a "nerve block"—on the injured nerve, effectively keeping any "bad signals" from reaching the brain. However, a single-injection block lasts less than 24 hours; and, even a continuous peripheral nerve block is generally limited to less than one week. The negative pain signals from the surgical insult continue for multiple weeks or months. In contrast to local anesthetic-induced nerve blocks, a prolonged block lasting a few weeks/months may be provided by freezing the nerve using a process called "**cryoneurolysis**". *The ultimate objective of the proposed line of research is to determine if cryoanalgesia is an effective adjunctive treatment for pain in the period immediately following mastectomy or limb amputation; and, if this analgesic modality decreases the risk of persistent postoperative pain, or "chronic" pain.* ***The objective of the proposed pilot study is to optimize the protocol and collect data to power subsequent, definitive clinical trials.***

6. SPECIFIC AIMS

The ultimate objective of the proposed line of research is to determine if cryoanalgesia is an effective adjunctive treatment for pain in the period immediately following various painful surgical procedures; and, if this analgesic modality decreases the risk of persistent postoperative pain, or "chronic" pain. ***The objective of the proposed pilot study is to optimize the protocol and collect data to power subsequent, definitive clinical trials.***

Specific Aim 1: **To determine if, compared with current and customary analgesia, the addition of cryoanalgesia decreases the *incidence* and *severity* of post-surgical pain.**

Hypothesis 1a (primary): The *severity* of surgically-related pain will be significantly decreased on postoperative day 2 with the addition of cryoanalgesia as compared with patients receiving solely standard-of-care treatment.

Hypothesis 1b: The *incidence* of chronic pain will be significantly decreased one year following surgery with the addition of cryoanalgesia as compared with patients receiving solely standard-of-care treatment.

Hypothesis 1c: The *severity* of chronic pain will be significantly decreased one year following surgery with the addition of cryoanalgesia as compared with patients receiving solely standard-of-care treatment.

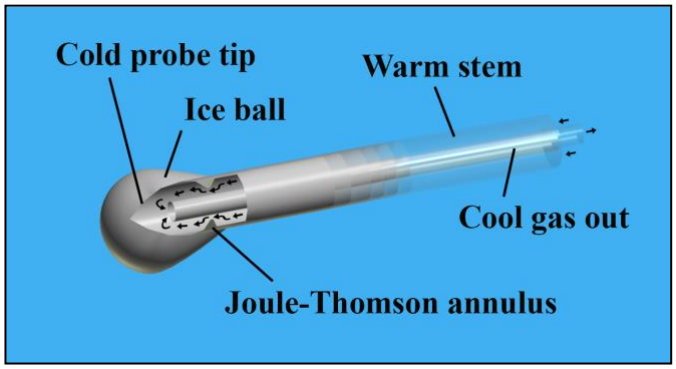
Specific Aim 2: **To determine if, compared with current and customary analgesia, the addition of cryoanalgesia improves postoperative functioning.**

Hypothesis 2a: Following primary unilateral knee and shoulder arthroplasty as well as rotator cuff repair, joint range of motion will be significantly increased within the year following surgery with the addition of cryoanalgesia as compared with patients receiving solely standard-of-care treatment.

Hypothesis 2b: Following video-assisted thoracoscopic surgery, inspiratory spirometry will be improved within the month following surgery with the addition of cryoanalgesia as compared with patients receiving solely standard-of-care treatment.

7. BACKGROUND AND SIGNIFICANCE

Hypothesis 1a (acute pain): Pain within the first week after a mastectomy or limb amputation is often intense, with breakthrough pain as measured with a Numeric Rating Score (NRS; 0-10, 0 = no pain, 10 = extreme pain) a median of 7; and 25% of women describing a “continuous aching pain” the day following mastectomy.[1] Similarly, pain following knee and shoulder arthroplasty, rotator cuff repair, video-assisted thoracoscopic surgery, and burn-related skin grafting also can result in significant postoperative pain. Intense analgesia may be provided with a peripheral nerve block, which involves the placement of long-acting local anesthetic adjacent to the peripheral nerves that innervate the surgical site.[2] Unfortunately, the longest-acting local anesthetics clinically available have a duration of less than 24 hours, after which patients are mainly dependent upon opioids, which result in inadequate analgesia and undesirable side effects such as pruritis, nausea, vomiting, constipation, urinary retention, sedation, and respiratory depression. Local anesthetic-based analgesia may be extended using a continuous perineural infusion via a percutaneous catheter; but, this technique is usually limited to a few days due to infection risk, catheter dislodgement, and anesthetic consumption.[3] The pain of these surgical procedures can last weeks, and is often exacerbated by physical therapy, itself critical to optimizing outcomes following knee and shoulder surgery.



An alternative analgesic technique is <u>cryoneurolysis,</u> consisting of the application of exceptionally low temperatures to *reversibly* ablate peripheral nerves, resulting in temporary pain relief termed "cryoanalgesia".[4] The intense cold temperature at the probe tip produces Wallerian degeneration—a reversible breakdown of the nerve axon—subsequently inhibiting transmission of afferent and efferent signals. Because the nerve endoneurium, perineurium, and epineurium remain intact, the axon regenerates along the exoskeleton at a rate of approximately 1-2 mm/day. While cryoneurolysis of peripheral nerves through surgical incisions has been commonly used to treat pain since 1961, the development of cryo probes that may be inserted percutaneously promise a revolution in the use of this modality. The combination of newly-designed narrow-gauge probes (immediate right) and ultrasound now make percutaneous cryoanalgesia as simple as placing a peripheral nerve block: the probe tip is inserted adjacent to the target nerve under ultrasound guidance, and a series of 1-minute freezing cycles are administered followed by probe withdrawal.[5] ***The procedure is essentially the same as placing an ultrasound-guided peripheral nerve block; however, instead of injecting local anesthetic, a gas circulates through the probe, inducing cold at the tip and freezing the target nerve.*** Nothing remains within the patient and there is no external equipment to prepare or manage. Importantly, cryoneurolysis and the cryo probes are already approved by the United States Food and Drug Administration for the treatment of acute and chronic pain, so no additional regulatory approval is required for the proposed clinical trial.

Theoretical benefits of cryoneurolysis include an ultra-long duration of action without opioid involvement, no catheter management/removal, the lack of an infusion pump and anesthetic reservoir to carry, an extraordinarily-low risk of infection (approaching zero), and no risk of local anesthetic toxicity, catheter dislodgement or leakage. With a single 8-minute percutaneous cryoneurolysis procedure consisting of several freeze/defrost cycles, a truncation of sensory nerve conduction is induced for 6-8 weeks (motor neurons variable) with the complete restoration of nerve structure and function following remyelination. Cryoneurolysis offers the possibility of potent, side effect-free analgesia outlasting the surgical pain, and obviating the need for postoperative opioids.

Hypothesis 1b and 1c (persistent, post-surgical chronic pain): Following mastectomy and other painful surgical procedures, moderate to severe pain within the acute postoperative period is closely associated with subsequent persistent postsurgical pain lasting months[6] or even years.[7,8] Such chronic pain has an incidence of 30-73%,[8-10] and is strongly correlated with depression and anxiety.[11] There is evidence that intense analgesia immediately following surgery may decrease the incidence and/or severity of chronic pain.[12,13] Potent analgesia can be provided with intercostal nerve blocks in which local anesthetic is percutaneously injected adjacent to the peripheral nerves innervating the

breast.[1,13] While single-injection nerve blocks have a duration of approximately 8 hours,[14] they have been associated with a lower incidence of chronic pain 4-12 months after mastectomy.[13,15,16] Extending the block to 60 hours can further decrease the incidence and severity of chronic pain.[17]

Furthermore, while the prevalence of post-mastectomy phantom breast pain—painful sensations perceived in the breast that is no longer present[18]—varies greatly, it has been reported as high as 44%.[9] There is prospective clinical evidence that following upper and lower extremity amputation, continuous brachial plexus, sciatic, and femoral nerve blocks may decrease the incidence and/or severity of phantom limb pain.[19,20] Using cryoneurolysis, a dense, multi-week peripheral nerve block may be provided, offering not only the possibility of the block outlasting the surgical pain, but enabling an opioid-free recovery and dramatically decreasing the risk of chronic pain.

Thirty-five to 98 percent of limb amputees (depending on the study) develop chronic, intractable pain perceived as being from the missing limb, a phenomenon termed "phantom pain".[20] The pain is usually described as "shooting, stabbing, boring, squeezing, throbbing, and burning".[21] Unfortunately, phantom pain resolves in only 16% of afflicted individuals (with or without treatment). The rest will experience phantom pain for the remainder of their lives, with most becoming dependent upon chronic opioid use to gain even a small degree of relief. There is currently no reliable, definitive treatment for phantom pain.

A "continuous peripheral nerve block"—administration of local anesthetic through a percutaneously-inserted perineural catheter—may provide a prolonged block.[3] In an uncontrolled series of 19 patients with phantom pain treated with continuous blocks, pain intensity was halved at 1 and 6 months.[20] However, the sensory block using this technique is frequently incomplete and/or inconsistent; the infusion duration usually limited to less than one week due to the risk of infection and difficulty of carrying a large bag of local anesthetic; and catheter dislodgement is relatively common.[3] A more reliable, complete block of longer duration would theoretically increase any treatment effects for phantom pain, while reducing these inconveniences and complications. Cryoneurolysis offers such a dense, multi-week peripheral nerve block.

Given chronic pain's enormous costs to individuals and society—and the intractable, currently-untreatable nature of chronic pain with concurrent opioid dependence—it is imperative that an effective prevention strategy be developed. If our study demonstrates that ultrasound-guided percutaneous cryoneurolysis prevents chronic pain, the resulting impact on patients will be **immediate and profound**, as (1) healthcare providers within the United States already have expertise placing ultrasound-guided peripheral nerve blocks; (2) cryoneurolysis is a relatively inexpensive, single-procedure treatment with few complications; and (3) cryoanalgesia is already approved by the United States Food and Drug Administration.

8. PROGRESS REPORT

We have performed 3 cases in which cryoneurolysis was performed in the perioperative period for surgical limb amputation. Ultrasound-guided percutaneous cryoneurolysis was performed in a total of 3 patients: (1) preoperative femoral and sciatic nerve cryoneurolysis in a patient who underwent below-the-knee amputation, (2) postoperative cryoneurolysis to the sciatic and femoral nerves in a patient who underwent above-the-knee amputation, and (3) preoperative cryoneurolysis to the median, ulnar, and superficial radial nerve in a patient who underwent left partial hand amputation. All procedures utilizing ultrasound guidance were performed with a 5.5 cm probe introduced through a 16 or 20G angiocatheter.

All three patients experienced significant pain relief immediately, continuing for at least 2 weeks post-intervention. Numeric Rating Scale pain scores were consistently improved, ranging from 0 to 3 for multiple weeks. For the below-the-knee amputation, the patient had no postoperative pain when resting and only mild pain with activity without the use of any additional analgesics. The former two did not require long-term opioids and had no problems using their lower limb prosthesis two months following amputation. Only mild, transient phantom sensations were experienced in one patient. No adverse events associated with cryoanalgesia were reported in any of the patients.

9. RESEARCH DESIGN AND METHODS

All subjects would continue to receive standard and customary postoperative analgesics, so there is no risk of subjects receiving a lower degree of analgesia than if they otherwise did not enroll in the study. The cryoneurolysis procedure will be done in addition to our current UCSD standard practice.

Study Overview

Day 0 Subjects randomized and cryoneurolysis/sham procedure administered

Days 0-4, 7, 14, 21 Pain levels, opioid consumption, and other end points collected [inspiratory spirometry for hospitalized subjects following video-assisted thoracoscopic surgery will occur at various time points as part of standard care and will be collected via EPIC]

Months 1, 3, 6, 12 Brief pain inventory administered [range-of-motion measurements following knee and shoulder arthropscopy as well as rotator cuff repair will occur at various time points as part of standard care and will be collected via EPIC]

Year 3 Cancer recurrence investigated for subjects with cancer-related procedures

Subjects will be individuals undergoing unilateral or bilateral mastectomy; upper or lower limb amputation; primary, unilateral total knee or shoulder arthroplasty; primary, unilateral rotator cuff repair; video-assisted thoracoscopic surgery; and burn-related skin grafting of the lateral thigh. Those who consent to participate in this study will have standard preoperative peripheral nerve blocks administered and catheters inserted: paravertebral blocks or a fascial plane block (e.g., erector spinae plane block) for mastectomy, femoral/sciatic for lower limb amputation, brachial plexus (or terminal nerves) for upper limb amputation; femoral or adductor canal for total knee arthroplasty; interscalene for shoulder arthroplasty or rotator cuff repair; thoracic epidural for video-assisted thoracoscopic surgery (VATS); and lateral femoral cutaneous nerve for skin grafting of the lateral thigh.

Treatment group assignment (randomization). Subjects with successfully-administered peripheral nerve blocks (defined by sensory changes in the appropriate nerve distribution) will be allocated to one of two possible treatments:

1. *cryoneurolysis*
2. *sham cryoneurolysis (placebo control)*

Randomization will be stratified by surgery type (e.g., mastectomy, upper limb amputation, and lower limb amputation). Computer-generated randomization lists will be used to create sealed, opaque randomization envelopes with the treatment group assignment enclosed in each envelope labeled with the randomization number.

The specific nerves targeted will depend on the surgical site: intercostal nerves (4 levels depending on the specific surgical approach) for mastectomy; femoral/sciatic for lower limb amputation,brachial plexus (or terminal nerves) for upper limb amputation; infrapatellar branch of the saphenous nerve for knee arthroplasty; suprascapular nerve for shoulder surgery; intercostal nerves for VATS procedures, and the lateral femoral cutaneous nerve for skin grafting of the lateral thigh. The cryoneurolysis sites will be cleansed with chlorhexidine gluconate and isopropyl alcohol. Using the optimal ultrasound transducer for the specific anatomic location and subject anatomy (linear vs curvilinear array), the target nerves will be identified in a transverse cross-sectional (short axis) view.

Cryoneurolysis probes are available for a console neurolysis device (PainBlocker, Epimed, Farmers Branch, Texas) that either (1) pass nitrous oxide to the tip inducing freezing temperatures; or, (2) vent the nitrous oxide at the base of the probe so that no gas reaches the probe tip, resulting in no temperature change. Importantly, these probes are indistinguishable in appearance, and therefore treating physicians, subjects, and all clinical staff will be masked to treatment group assignment [only the physician/investigator performing the cryoneurolysis with be unmasked]. An angiocatheter/introducer may be inserted beneath the ultrasound transducer and directed until the probe tip is immediately adjacent to the target nerve (lidocaine 2% will be administered, as needed, to anesthetize the angiocatheter track). The angiocatheter needle will be removed, leaving the angiocatheter through which the appropriate Epimed probe will be inserted until it is adjacent to the target nerve. The cryoneurolysis device will be triggered using 3 cycles of 2-minute gas activation (active or sham) separated by 1-minute defrost periods. For active probes, the nitrous oxide will be deployed to the tip where a drop in temperature to -70°C will result in cryoneurolysis. For the sham probes, the nitrous oxide will be vented prior to reaching the probe shaft, resulting in a lack of perineural temperature change. The process will be repeated with the same treatment probe for any additional nerves (e.g., all nerves will receive either active cryoneurolysis or sham/placebo, and <u>not</u> a mix of the two possible treatments).

FDA Approval. Cryoneurolysis has been FDA approved since May 28, 1976, with continuous clinical use since then. The specific device used for this study, the Epimed Painblocker, has been FDA cleared for use to treat both acute and chronic pain since April 30, 1986, as a significant risk device. The Painblocker is NOT considered experimental or investigational (there is no IDE); and, we are using the device in a manner that the FDA approved of regarding the subject population and purpose (treating acute pain).

Outcome measurements (end points). Staff blinded to treatment group assignment will perform all measures and assessments, which will include:

Pain: measured on the 11-point NRS of pain intensity

Brief Pain Inventory: The Brief Pain Inventory (short form) is an instrument specifically designed to assess pain and its impact on physical and emotional functioning within the previous 24 hours.[22,23] It has established reliability and validity, with minimal inter-rater discordance, and is recommended by

the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.[24] The Brief Pain Inventory is comprised of three domains: (1) *pain,* with four questions involving "worst", "average", "least", and "current" pain levels using a 0-10 Numeric Rating Scale (NRS; 0 = no pain; 10 = worst pain imaginable); (2) percentage of *relief* provided by pain treatments with one question (reported score is the percentage divided by 10 and then subtracted from 10: 0 = complete relief, 10 = no relief); and, (3) *interference* with 7 questions involving physical and emotional functioning using a 0-10 Likert scale (0 = no interference; 10 = complete interference). The use of both single items (e.g., average pain) and the composite score (0 = optimal; 120 = worst possible) is supported by the IMMPACT recommendations for assessing pain in clinical trials.[25-27]

Opioid consumption

Sleep disturbances: due to surgical pain

Range of motion: measured with a standard goniometer

Forced expiratory volume in 1 second (FEV1): measured with a standard inspiratory spirometer

Cancer recurrence: for subjects who underwent the surgical procedure related to a primary cancer, subjects' records will be investigated for indications of cancer recurrence up to 3 years following catheter placement (including estrogen receptor status as + or -). Patients may be contacted by phone if records suggest that the patient has not returned to the original surgeon within the previous 12 months.

The questionnaire will differentiate among multiple dimensions of breast and limb pain:

Phantom pain: painful sensations referred to the lost body part (breast or limb).
Phantom breast/limb sensations: *non*-painful sensations referred to the lost body part.
Wound pain: painful sensations localized to the portion of the body still present.

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

Time Point:	Postoperative **Days**								Postoperative **Months**			
	0	1	2	3	4	7	14	21	1	3	6	12
Opioid consumption	•	•	•	•	•	•	•	•	•	•	•	•
Average & worst pain [NRS]	•	•	•	•	•	•	•	•				
Brief Pain Inventory									•	•	•	•
Average & worst phantom pain									•	•	•	•
Incidence; duration each episode									•	•	•	•
Average & worst wound pain									•	•	•	•
Incidence; duration each episode									•	•	•	•

Difficulty sleeping due to pain?		•	•	•	•	•	•	•				
Awakenings due to pain		•	•	•	•	•	•	•				
Nausea (0=none, 10=vomited)		•	•	•	•	•	•	•				

* In addition to the above, for knee and shoulder surgery joint range of motion will be measured at various time points between 1-12 months as part of standard postoperative care; and for VATS, FEV1 will be measured at various time points during hospitalization as part of standard postoperative care.

Statistical Analysis. The limb amputation, total knee and shoulder arthroplasty, rotator cuff repair, VATS, and skin grafting subjects will be included in pilot studies to help power future clinical trials, so we will enroll a convenience sample and not have a pre-determined primary endpoint or statistical plan. However, the end points of most interest will be average pain score on postoperative day 2 for shoulder arthroplasty and skin grafting subjects, range-of-motion at 6 weeks for the rotator cuff repairs, range-of-motion for knee arthroplasty, and FEV1 for the VATS procedures.

For the subjects having mastectomy, we will power this study for an acute pain end point which will provide conclusive results for that end point; but, the data will also be used to help power a subsequent large, multicenter clinical trial for a chronic pain-related end point (which will require far more subjects than we will enroll for the current study).

For the mastectomy subjects, sample size calculations are centered around the hypothesis that cryoneurolysis decreases the incidence and severity of post-mastectomy pain in the week following surgery. To this end, the primary outcome is the average NRS (as administered as part of the Brief Pain Inventory) queried on the afternoon of postoperative day 2. The difference in the distribution of NRS between groups will be assessed using the Mann-Whitney U test. We approximate power using the two-sample t-test. Assuming a standard deviation of 2.25 NRS points,[2] and minimum clinically meaningful difference of 2 NRS points, n=30 patients per group provide 86% power with two-sided α=5%.

The t-test approximation was confirmed by simulating integer valued NRS scores in the range 0 to 10. One group was simulated by rounding normally distributed data with mean 1.5 and standard deviation 2.5 (resulting in median of 2 and interquartile range 0 to 3); and the other with mean 3.5 and standard deviation 2.5 (resulting in median of 4 and interquartile range 1 to 5). Note these resulting summary statistics are consistent with Ilfeld et al (2014). When 10,000 trials were simulated under these assumptions, the Mann-Whitney U test provided 89.5% power, and Type I error was maintained at 4.85%.

Differences between groups in demographic variables and secondary endpoints will be assessed with the Mann-Whitney U test for continuous or ordinal data, and Fisher's Exact test for categorical data. Box-and-whisker plots will be used to visualize distributions by group.

R version 3.4.4 (R-project.org) was used for sample size calculations and simulations; and the most recent version of R will be used at the time of analysis.

10. HUMAN SUBJECTS

A convenience sample of subjects undergoing limb amputation (n=60), mastectomy (n=60), knee arthroplasty (n=60), shoulder arthroplasty and rotator cuff repair (n=60), VATS (n=60), and skin grafting of the lateral thigh (n=60) will be enrolled, with an additional 20 permitted to replace drop-outs. This will total up to 380 subjects.

Inclusion criteria: Adult patients of at least 18 years of age, (1) scheduled for a primary, unilateral total knee or shoulder arthroplasty, primary unilateral rotator cuff repair, VATS procedure, skin grafting of the lateral thigh, unilateral or bilateral mastectomy, or limb amputation distal to the femoral/humeral head and including at least one metatarsal/metacarpal bone; (2) a single-injection or continuous peripheral nerve block or epidural infusion planned for perioperative analgesia; and, (3) accepting of a cryoneurolysis procedure.

Exclusion criteria: (1) chronic opioid use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks); (2) pregnancy; (3) incarceration; (4) inability to communicate with the investigators; (5) morbid obesity (body mass index > 40 kg/m^2); and, (6) possessing any contraindication specific to cryoneurolysis such as a localized infection at the treatment site, cryoglobulinemia, cold urticaria and Reynaud's Syndrome.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Study inclusion will be proposed to eligible patients in a preoperative surgical or anesthesia-related visit or phone call within four weeks prior to surgery—either by the surgeon or anesthesiologist, both investigators and involved in the patient's clinical care (HIPAA requirements will be adhered to). If a patient desires study participation, written, informed consent will be obtained using an IRB-approved informed consent form. Selection for inclusion will not be based on sex, race or socioeconomic status. For women of childbearing age with the possibility of pregnancy, a sample of urine is always collected for a pregnancy test prior to surgery—regardless of study participation. Pregnant patients will be excluded from study participation.

12. INFORMED CONSENT

When a prospective subject desires, they will be provided information on the study purpose and protocol, as well as have any questions answered. Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled for their initial treatment. Written informed consent will be attained prior to any measurements or procedures the morning of surgery. This will occur in private patient care rooms, so that subjects may feel comfortable asking questions.

We do not foresee any issues relevant to the mental capacity of the potential human subjects. Written, informed consent will be attained prior to any study procedures or measurements. Following a history and physical by the site director, subjects will have an intravenous line inserted, external monitors placed, oxygen delivered by face mask, and conscious sedation provided for perineural catheter insertion. Therefore, subjects will not be sedated until following the written, informed consent process is completed.

Subjects 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 room to again review the study, informed consent form, and answer any remaining subject questions. As noted previously, subjects may speak with an investigator by telephone from initial contact through the morning of treatment.

Surrogate consent will not be accepted; therefore, if human subjects 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. Of note, minors (age < 18 years) will not be offered enrollment. Therefore, assent will not be accepted during the informed consent process.

13. ALTERNATIVES TO STUDY PARTICIPATION

Potential study subjects may simply decline enrollment. They will still receive our standard-of-care analgesics including a continuous peripheral nerve block.

14. POTENTIAL RISKS

1. Infection. There is the potential risk of infection since subjects will have a probe inserted through the skin. Since there will be nothing left going through the skin or in the subject after the probe is withdrawn, the risk of infection is very small and there has never been a report of permanent injury due to infection following cryoneurolysis.
2. Bleeding. The probe does not have an open tip and is not particularly sharp, so there is a very low risk of having any type of bleeding as a result of treatment. However, if it was to happen, we would hold pressure until the bleeding stopped.
3. The skin where the nerve is frozen could lose or gain color if the nerve is particularly close to the surface. However, this has never been reported for deeper nerves and using the probe that will be used for this study.
4. Since a nerve will be frozen, there is the chance of nerve injury. However, in 5 decades of using cryoneurolysis on peripheral nerves, only a single case of "neuritis" (nerve irritation) has been reported in medical journals, and this resolved after a few months.
5. There is the risk of loss of confidentiality. The following procedures will be done to maintain confidentiality: written, paper forms will be kept in a locked medical office and the locked Investigational Pharmacy's files. Computerized records containing personal health information will be stored on password-protected and encrypted computers.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

During the treatment, subjects will be continuously monitored with pulse oximetry, noninvasive blood pressure cuffs, and EKG (standard for catheter placement). Subjects will receive an IV so that emergency medications could be given, if needed. As described above, probes will be placed under sterile conditions as is standard-of-care for any percutaneous cryoneurolysis.

Following treatment, the subjects will be contacted daily for the first 4 days, and then on days 7, 14, 21, 28 as well as months 3, 6, and 12. Subjects will have a physicians' pager and cellular phone numbers available to respond 24 hours/day and 7 days/week for at least the first week following treatment.

The risks to confidentiality are the release of names/ telephone numbers/ demographic data (e.g. weight, age, height), which will be minimized by the use of password-protected computers and case report forms that will be stored in locked offices.

Subjects will be given clear instructions to call an investigator with any questions or concerns regarding their study participation. If a patient experiences an injury that is directly caused by this study, only professional medical care that they receive at the medical center. No other compensation is offered. Any adverse events will be reported to the IRB using the standard adverse events

reporting and upon continuing review (depending on severity, as defined by the IRB).

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Disposition of data. The original, hard-copy signed informed consent forms and case report forms will be stored within an investigator's locked office; and they will remain with the Principal Investigator for at least 7 years. Data will be entered into an Excel spreadsheet kept on a password-protected and encrypted computer and retained by the Principal Investigator for at least 7 years.

17. POTENTIAL BENEFITS

For subjects randomized to receive a sham treatment: There will be no difference between being in this study and deciding against participation. Therefore, there is no potential for direct benefits from this sham "treatment".

For subjects randomized to receive active cryoneurolysis: It is our hope that patients have a decrease in their acute and chronic postoperative pain (which might permit a decreased opioid consumption and opioid-related nausea/vomiting).

Possible benefits to others: Future patients may benefit if it is determined that cryoneurolysis decreases postoperative pain. In addition, with the opioid epidemic, any decrease in opioid requirements would be a welcome development.

18. RISK/BENEFIT RATIO

Chronic phantom limb and residual limb pain cause significant disability for patients, and there is currently a dearth of reliable treatments for this debilitating pain. Since cryoneurolysis has a very low incidence of complications, and there have no previous cases of permanent negative sequelae reported in the literature, we believe the potential risks to be minimal compared to the potential benefits.

Subjects will be given clear verbal and written instructions to call Dr. Ilfeld in the Department of Anesthesia at UCSD, with any questions or concerns regarding their study participation. If a patient experiences an injury that is directly caused by this study, they will receive professional medical care at the University of California, San Diego. No other compensation is offered. Any adverse events will be reported to the UCSD IRB using the standard adverse events reporting website and on continuing review (depending on severity, as defined by the IRB).

19. EXPENSE TO PARTICIPANT

There will be no additional costs to subjects as a result of being in this study.

20. COMPENSATION FOR PARTICIPATION

There is no compensation for participation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator, **Brian M. Ilfeld, MD, MS,** is a board-certified anesthesiologist with fellowship training in and 17 post-training years experience with regional anesthesia and acute pain medicine. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC Medical Centers. Dr. Ilfeld, or another investigator, will follow all subjects following their treatment. Dr. Ilfeld will be responsible for the overall management of this study, as well as for the well-being of

study subjects.

Co-investigators, **Rodney Gabriel, MD, Wendy Abramson, MD, Jessica Black, MD, John Finneran, MD, Bahareh Khatibi, MD, Engy Said, MD, Jackie Sztain, MD, and Matthew Swisher, MD,** are board-certified or -eligible anesthesiologists with experience with regional anesthesia and acute pain medicine. All hold a license to practice medicine in California and medical privileges at the UC Medical Centers. All will help consent subjects, perform a history and physical exam, perform the treatment on subjects, and will follow subjects following their treatment. In addition, **Anne Wallace, MD,** is a board-certified surgeon with decades of experience performing mastectomies, holds a license to practice medicine in California and medical privileges at the UC Medical Centers, and will help enroll subjects, perform her history and physical exam, perform the surgical procedures, and follow-up with subjects.

Baharin Abdullah and **Jeffrey Mills** are research coordinators with the UCSD CTRI, with the required training—including up-to-date CITI training—for their positions.

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23. FUNDING SUPPORT FOR THIS STUDY

The companies Epimed and Myoscience have provided our department with 2 unrestricted research grants which may be used at our discretion; and we will use some of these funds to support this study. In addition, we will be using Epimed and Myoscience cryoneurolysis machines/probes on loan from the companies for this study.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable since percutaneous cryoneurolysis and the products used for this protocol are all cleared by the United States Food and Drug Administration for use treating both acute and chronic pain. Therefore, this is an on-label study.

26. IMPACT ON STAFF

Participants will be enrolled by investigators and research coordinators specifically hired and trained for the study. No other staff are required for this study, and therefore there will not be an impact on hospital staff.

27. CONFLICT OF INTEREST

The companies Epimed and Myoscience have provided our department with 2 unrestricted research grants which may be used at our discretion; and we will use some of these funds to support this study. In addition, we will be using Epimed and Myoscience cryoneurolysis machines/probes on loan from the companies for this study. Dr. Ilfeld completed a study with Myoscience 2 years ago, but did not receive any funding directly (funding was sent to the University of California Regents for support of the research). No investigator has any other financial relationship with either of these companies.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES

Not applicable.

29. OTHER APPROVALS/REGULATED MATERIALS

None.

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

Not applicable: surrogate consent will not be accepted.