**Official Title:** Cryoanalgesia to Treat Phantom Limb Pain following a Trans-Femoral (Above-Knee) Amputation: A Randomized, Sham-Controlled Pilot Study

**NCT:** 06071715

**Document date:** December 11, 2023

# Cryoanalgesia to Treat Phantom Limb Pain following a Trans-Femoral (Above-Knee) Amputation: A Randomized, Sham-Controlled Pilot Study

**Protocol Number: 808845**

**National Clinical Trial (NCT) Identified Number: NCT06071715**

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**Funded by: The U.C. San Diego Department of Anesthesiology**

**Protocol: Version 1.2**

**11-Dec-2023**

## Summary of Changes from Previous Version:

| Affected Section(s) | Summary of Revisions Made | Rationale |
|---|---|---|
| 10.2.3(page36) | Increase in subject compensation from $200 to $750. | We are increasing subject compensation from $200 to $750. We have participants from around the country who are interested in participating in the study, but participants can't afford to travel. We recently received the Senate grant, so now we can afford to increase the compensation. |
| | | |

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# 1 PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **Title:** | **Cryoanalgesia to Treat Phantom Limb Pain following a Trans-Femoral (Above-Knee) Amputation: A Randomized, Sham-Controlled Pilot Study** |
| **Study Description:** | The study is a single-center, randomized, participant- and observer-masked, active-controlled, parallel-arm (optional crossover), human-subjects, post-market clinical pilot study to investigate the use of ultrasound-guided percutaneous cryoneurolysis to treat phantom limb pain following a trans-femoral (above-knee) amputation. A prolonged nerve block may be provided by freezing the nerve using a technique called "cryoneurolysis". With cryoneurolysis and ultrasound machines, a small needle-like "probe" may be placed through anesthetized skin and guided to the target nerve to allow freezing. The procedure takes about 6 minutes for each nerve, involves little discomfort, has no systemic side effects, and cannot be misused or become addictive. After 2-3 months, the nerve returns to normal functioning. Participants will be randomly allocated to one of two possible treatments groups: cryoneurolysis (experimental) or sham (control). The primary outcome measure is the change in the phantom limb pain intensity from baseline 1 month following the procedure as measured by the Numeric Rating Scale within the Brief Pain Inventory. |
| **Objectives:** | The ultimate objective of the proposed research study is to demonstrate feasibility and estimate the treatment effect of using cryoanalgesia as a treatment for intractable phantom limb pain following a trans-femoral (above-knee) amputation to assist in determining the required sample size of a subsequent definitive clinical trial.<br><br>***Primary Specific Aim:*** **To test the influence of a cryoanalgesia treatment as compared to sham/placebo on the intensity of existing, intractable phantom limb pain resulting from an above-knee amputation.**<br><br>***Hypothesis 1:*** Phantom limb pain ***intensity*** will be decreased relative to baseline 1 month following a cryoneurolysis procedure (as measured by the Numeric Rating Scale within the Brief Pain Inventory).<br><br>***Secondary Specific Aim:*** **To test the influence of a cryoanalgesia treatment as compared to sham/placebo on the quality of life for individuals with intractable phantom limb pain resulting from an above-knee amputation.**<br><br>***Hypothesis 2a:*** Perception of **well-being** will be improved 1 month following one cryoneurolysis procedure (as measured with the Patient Global Impression of Change Scale).<br><br>***Hypothesis 2b:*** Physical and emotional **functioning** will be improved relative to baseline 1 month following one cryoneurolysis procedure (as measured with the Interference Subscale of the Brief Pain Inventory). |

**Endpoints:**

***Hypothesis 1:*** Phantom limb pain ***intensity*** will be decreased relative to baseline 1 month following a cryoneurolysis procedure (as measured by the Numeric Rating Scale within the Brief Pain Inventory).

***Hypothesis 2a:*** Perception of **well-being** will be improved 1 month following one cryoneurolysis procedure (as measured with the Patient Global Impression of Change Scale).

***Hypothesis 2b:*** Physical and emotional **functioning** will be improved relative to baseline 1 month following one cryoneurolysis procedure (as measured with the Interference Subscale of the Brief Pain Inventory).

**Table 1. Summary of post-enrollment assessments.**

* The second—or "crossover"—treatment intervention will occur between 4-6 months following the initial treatment

| **Subjects:** | **All** | | | | | | | **Participating in Crossover *** | | | | | | | **All** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time Point Following:** | **Initial** Treatment | | | | | | | **Crossover** Treatment | | | | | | | **Initial** |
| **Time Point (Days):** | 0 | 1 | 7 | | | | | 0 | 1 | 7 | | | | | |
| **Time Point (Months):** | | | | 1 | 2 | 3 | 4 | | | | 1 | 2 | 3 | 4 | 12 |
| Phantom Limb Pain (worst, least, average, current), NRS | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Residual Limb Pain (worst, least, average, current), NRS | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Patient Global Impression of Change Scale | | • | • | • | • | • | • | | • | • | • | • | • | • | • |
| Brief Pain Inventory Interference Scale | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Non-Painful Phantom Sensations (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Phantom Limb Pain (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Residual Limb Pain (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |

**Study Population**

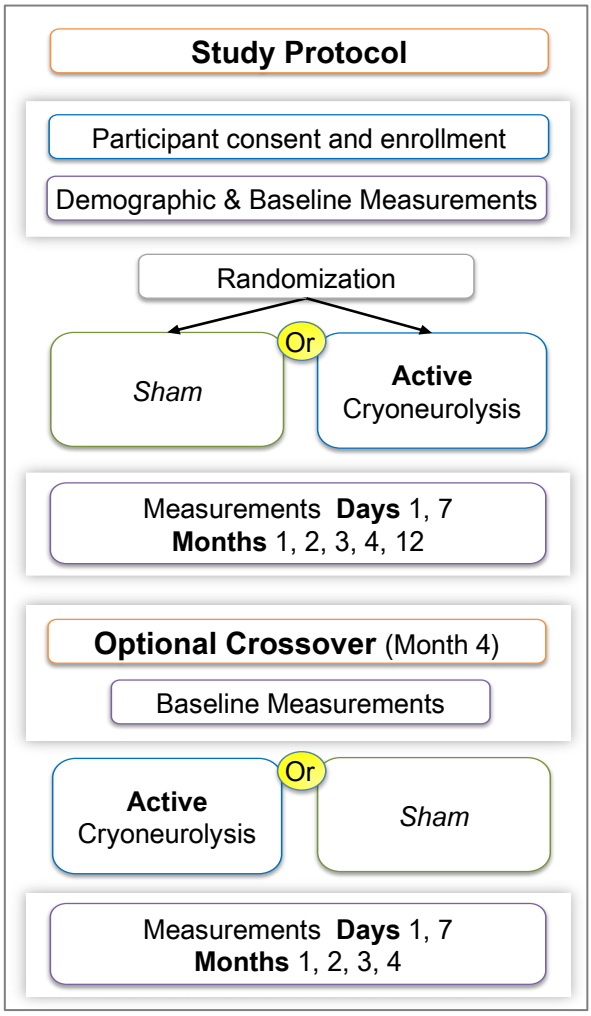
There will be approximately 25 participants.

**Inclusion criteria:**

| | |
|---|---|
| | (1) Adult patients of at least 18 years of age<br>(2) Trans-femoral traumatic or surgical amputation at least 12 weeks prior to enrollment distal to the hip (femoral head remaining)<br>(3) Experiencing at least moderate phantom limb pain—defined as a 4 or higher on the Numeric Rating Scale (NRS; 0-10, 0= no pain; 10=worst imaginable pain)—at least daily for the previous 2 months<br>(4) willing to avoid both changes to their analgesic regimen as well as elective surgical procedures from 1 month prior to and at least 4 months following the initial cryoneurolysis procedure.<br><br>**Exclusion criteria:**<br>(1) allergy to amide local anesthetics<br>(2) pregnancy<br>(3) incarceration<br>(4) inability to communicate with the investigators<br>(5) morbid obesity (body mass index > 40 kg/$m^2$)<br>(6) possessing any contraindication specific to cryoneurolysis such as a localized infection at the treatment site, cryoglobulinemia, cold urticaria and Reynaud's Syndrome |
| **Phase:** | Not applicable to this investigation involving a medical device (as opposed to a medication) |
| **Description of Sites/ Facilities Enrolling Participants** | U.C. San Diego Clinical and Translational Research Institute |
| **Description of Study Intervention** | **Treatment group allocation (randomization).** Participants will be allocated to one of two possible treatments groups:<br>***1. Cryoneurolysis***<br>***2. Sham (Control)***<br><br>The cryoneurolysis sites will be cleansed with chlorhexidine gluconate and isopropyl alcohol. ***The nerves treated will include the femoral, sciatic, obturator, and lateral femoral cutaneous***. Each nerve will be visualized using ultrasound, a skin wheal of local anesthetic will be raised inferior to the transducer to anesthetize the skin and then the track towards the target nerve. The probe will then be inserted adjacent to the target nerve. The cryoneurolysis machine (CryoCare, Varian Medical Systems, Palo Alto, California) uses argon for the freeze cycle and helium to help decrease the thaw period duration. The cryoneurolysis device will be triggered using 1 cycle of 5.5-minute argon activation (2000-2500 PSI and 100% power) followed by a 30-second helium defrost. The Varian machine provides its own timer so that the gas cycle timing is precise to the second. This may be repeated, as necessary, to ensure the entire cross-section of each nerve is fully treated.<br><br>**Active Cryoneurolysis.** For participants randomized to active treatment, the probe placed in the patient will be triggered and the argon (and helium) passed through the probe and then back into the machine, and finally vented out from the console. This will result in a freeze-thaw cycle. |

| | |
|---|---|
| | **Control.** For participants randomized to sham treatment, the probe in the patient will simply not be activated; instead, a second probe that is not inserted in the patient will be triggered which will create the same visual and auditory cues as for the active participants retaining the masked feature. The investigator administering the study intervention will activate the correct probe depending on the treatment group assignment. Therefore, all investigators and participants will be masked to treatment group assignment, with the only exception being the unmasked investigator who performs the procedure (and will not have subsequent contact with the participant).<br><br>It is impossible to mask the individual performing the cryoneurolysis procedure because the ice ball forming at the distal end of the probe—with active treatment—is clearly visible by ultrasound; and the lack of an ice ball for sham participants is equally clear. It is essential to continuously visualize the probe and target nerve throughout the freeze/thaw cycle(s) to ensure the entire nerve diameter is adequately treated and remains relatively motionless. This cannot be achieved if the ultrasound is turned off during nitrous oxide or argon administration to mask the provider; and we prioritize patient safety over masking of the physician administering the intervention.<br><br>**FDA Approval.** Cryoneurolysis has been FDA approved since May 28, 1976, with continuous clinical use since then. The specific deviceused for this study, the Varian CryoCare has been FDA cleared for use to treat both acute and chronic pain since August 11, 2020, as a significant risk device. We are therefore using the device in a manner that the FDA approved of regarding the participant population and purpose (treating acute pain), and no FDA IDE is required. |
| **Study Duration:** | Approximately 2 years (including follow-up and analysis). |
| **Participant Duration:** | Approximately 12 months |

## 1.2 SCHEMA




## 1.3 SCHEDULE OF ACTIVITIES (SOA)

| Subjects: | All | | | | | | | Participating in Crossover * | | | | | | | All |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time Point Following: | Initial Treatment | | | | | | | Crossover Treatment | | | | | | | Initial |
| Time Point (Days): | 0 | 1 | 7 | | | | | 0 | 1 | 7 | | | | | |
| Time Point (Months): | | | | 1 | 2 | 3 | 4 | | | | 1 | 2 | 3 | 4 | 12 |
| Written Informed Consent | • | | | | | | | | | | | | | | |
| Screening for eligibility | • | | | | | | | | | | | | | | |
| Urine Pregnancy test ( as needed) | • | | | | | | | • | | | | | | | |
| Randomization | • | | | | | | | | | | | | | | |
| Conscious sedation and study treatment | • | | | | | | | • | | | | | | | |
| Phantom Limb Pain (worst, least, average, current), NRS | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Residual Limb Pain (worst, least, average, current), NRS | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Patient Global Impression of Change Scale | | • | • | • | • | • | • | | • | • | • | • | • | • | • |
| Brief Pain Inventory Interference Scale | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Non-Painful Phantom Sensations (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Phantom Limb Pain (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Residual Limb Pain (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |

# 2 INTRODUCTION

## 2.1 STUDY RATIONALE

When a limb is severed, pain perceived in the part of the body that no longer exists often develops and is called “phantom limb” pain. Unfortunately, phantom pain goes away in only 16% of afflicted individuals, and there is currently no reliable definitive treatment. The exact reason that phantom limb pain occurs is unclear, but when a nerve is cut—as happens with an amputation—changes occur in the brain and spinal cord that actually increase with worsening phantom pain. These abnormal changes may often be corrected by putting local anesthetic—called a “nerve block”—on the injured nerve, effectively keeping any “bad signals” from reaching the brain with a simultaneous resolution of the phantom limb pain. However, when the nerve block resolves after a few hours, the phantom pain

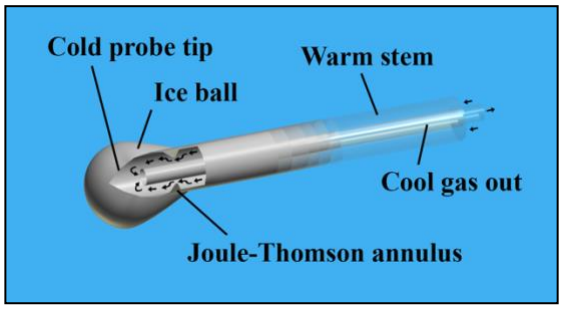
returns. But, this demonstrates that the brain abnormalities—and phantom pain—that occur with an amputation are not necessarily fixed, and may be dependent upon the "bad" signals being sent from the injured nerve(s), suggesting that a very long peripheral nerve block—lasting many months rather than hours—may permanently reverse the abnormal changes in the brain, and provide definitive relief from phantom pain. A prolonged nerve block lasting a few months may be provided by freezing the nerve using a process called "**cryoneurolysis**". ***The ultimate objective of the proposed research study is to demonstrate feasibility and estimate the treatment effect of using cryoanalgesia as a treatment for intractable phantom limb pain following a trans-femoral (above-knee) amputation to assist in determining the required sample size of a subsequent definitive clinical trial.*** The proposed research study will include subjects with an existing lower extremity amputation who experience intractable daily phantom limb pain. A single ultrasound-guided treatment of cryoneurolysis (or sham block—determined randomly like a flip of a coin) will be applied to the target nerve(s) involved with the phantom pain. Although not required, each subject may return four months later for the alternative treatment (if the first treatment is sham, then the second treatment would be cryoneurolysis) so that all participants have the option of receiving the active treatment. Subjects will be followed for up to 12 months with data collected by telephone.

## 2.2 BACKGROUND

Over 200,000 traumatic and surgical amputations occur annually within the United States alone; with an estimated 1.6-million people living with an amputation, and this number is expected to double by 2050. Among amputees, 35-98% (depending on the study) develop chronic, intractable pain perceived as being from the missing limb, a phenomenon termed "phantom limb pain". The pain is usually described as "shooting, stabbing, boring, squeezing, throbbing, and burning". 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 limb pain.

The exact reason that phantom limb pain occurs is unclear, but when a nerve is cut—as happens with an amputation—changes occur in the brain and spinal cord that increase with worsening phantom pain. These abnormal changes may often be corrected by putting local anesthetic—called a "nerve block"—on the injured nerve, effectively keeping any "bad signals" from reaching the brain with a simultaneous resolution of the phantom limb pain. However, when the nerve block resolves after a few hours, the phantom pain returns. But this demonstrates that the brain abnormalities—and phantom pain—that occur with an amputation are not necessarily fixed and may be dependent upon the "bad" signals being sent from the injured nerve(s). This, in turn, suggests that a very long peripheral nerve block—lasting many months rather than hours—may permanently reverse the abnormal changes in the brain and provide definitive relief from phantom pain. A prolonged nerve block lasting a few months may be provided by freezing the nerve using a process called "**cryoneurolysis**". **The ultimate objective of the proposed research study is to determine if cryoanalgesia is an effective treatment for intractable post-amputation phantom limb pain.**

**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". 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 cryoneurolysis devices (above right), the narrow-gauge probes (immediate right), and ultrasound[16,17] 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, the probe tip is frozen and subsequently withdrawn. **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 pain, including phantom limb 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 percutaneous cryoneurolysis procedure, nerve conduction is attenuated 2-3 months with the complete restoration of nerve structure and function following remyelination.

**<u>There is currently no reliable treatment for phantom limb pain</u>.** While more than 43 methods for treating phantom pain have been described, the placebo effect is common, and prolonged relief is experienced by fewer than 10% of treated patients (6% of untreated patients ultimately experience spontaneous resolution). Evidence of the intractable nature of phantom pain may be found in a survey of more than 10,000 amputees which reported a 1% treatment success rate. **Therefore, the overwhelming majority of people suffering from phantom limb pain are dependent upon <u>opioid analgesics</u> to gain even a small degree of relief.** There are few data from randomized trials to guide treatment, leading the authors of a major review to conclude that there remains a substantial "gap between research and practice in the area of phantom limb pain".

We have completed and published a Department of Defense-funded multicenter, randomized, double-masked, sham-controlled clinical trial investigating the use of ultrasound-guided percutaneous cryoneurolysis to treat existing post-amputation phantom limb pain (UCSD IRB 170973, now closed).[1] In short, patients who had a below-the-knee amputation (BKA) experienced prolonged benefit from active treatment (P=0.003); but patients who had an above-the-knee amputation (AKA) did not experience similar analgesia. Therefore, because the study was designed to analyze these two amputation levels together, the overall findings were negative (P=0.759). There is subsequently published evidence that the nitrous-oxide-based equipment that was used (PainBlocker, Epimed International, Dallas, TX) did not form a large or cold enough ice ball to adequately treat the larger nerves of the upper thigh for AKAs, resulting in a neuropraxia that worsened pain.[2] We theorize that the nitrous-oxide-based equipment that was used (PainBlocker, Epimed International, Dallas, TX) did not form a large or cold enough ice ball to adequately treat the larger nerves of the upper thigh for AKAs. In contrast, the ice ball size/temperature was adequate to treat the smaller nerves of the lower thigh for BKAs, resulting in cryoneurolysis and prolonged analgesia.

Given chronic pain's enormous costs to individuals and society—and the intractable, currently-untreatable nature of phantom limb pain with concurrent opioid dependence—it is imperative that an effective treatment be developed. If our study demonstrates that ultrasound-guided percutaneous cryoneurolysis is a successful treatment, the resulting impact on the hundreds-of-thousands of Americans suffering from intractable phantom limb pain will be **immediate and profound**, as (1) healthcare providers within the United States Armed Forces, Veterans Affairs Medical Centers, and civilian hospitals already have expertise placing ultrasound-guided peripheral nerve blocks; (2) cryoneurolysis is a relatively inexpensive, single-procedure, outpatient treatment with few complications; and (3) cryoanalgesia is already approved by the United States Food and Drug Administration.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

The procedures and devices used in this study are already 510k cleared by the United States Food and Drug Administration to provide postoperative analgesia. However, there may be risks that are not yet known, and the incidences provided are all estimated.

1. **Infection** (very low risk). There is the potential risk of infection since participants will have a probe inserted through the skin. Since there will be nothing left going through the skin or in the participant 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** (very low risk). 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** (very low risk). 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** (very low risk). Only a single case of "neuritis" (nerve irritation) has been reported in medical journals involving percutaneous cryoneurolysis, and this resolved after a few months.
5. **Falling.** The risk of falling due to cryoneurolysis in a lower extremity (leg) currently unknown, although it has never been reported in the medical journals.
6. **Pain**. Although we use local anesthetic to anesthetize the tissue as well as intravenous fentanyl, participants may experience discomfort or pain during the intervention.
7. **Sedation.** The sedation medication can result in itching, nausea, vomiting, sleepiness, constipation, and decreased depth and frequency of breathing.
8. **Intravenous line.** There is a very small chance that the intravenous line could become infected. If it was to become infected, the participant would be given antibiotics to treat the infection.
9. **There is the risk of loss of confidentiality** (low risk). 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.

### 2.3.2 KNOWN POTENTIAL BENEFITS

**For participants 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 participants randomized to receive active cryoneurolysis**: It is our hope that patients have a decrease in phantom and/or residual limb pain which might decrease supplemental analgesic consumption, analgesic-related side effects (e.g., opioid-related sedation), and interference of pain in physical and emotional functioning.

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

### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Chronic phantom pain causes significant disability for patients, and there is currently a dearth of reliable treatments for this debilitating pain. Even chronic pain described as "mild" has a significant negative impact on physical and mental health,[3,4] as well as substantially decreasing overall quality of life.[4-9]

In contrast, the risks of cryoneurolysis are minimal compared with the common treatment of a peripheral nerve block. There have no previous cases of permanent negative sequelae reported in the literature, and we therefore believe that the potential risks of cryoneurolysis are minimal compared to the potential benefits.

# 3 OBJECTIVES AND ENDPOINTS

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| **Primary** | | |
| To estimate the analgesic effect of cryoneurolysis on intractable post-amputation (trans-femoral) *phantom* limb pain 1 month post-treatment | *Phantom* limb pain intensity will be significantly decreased relative to baseline pain 1 month following a cryoneurolysis procedure (as measured by the Numeric Rating Scale within the Brief Pain Inventory). | Pain negatively influences physical and emotional functioning. |
| **Secondary** | | |
| To estimate the analgesic effect of cryoneurolysis on intractable post-amputation (trans-femoral) *phantom* limb pain at various time points post-treatment (Days 1, 7, and Months 2, 3, 4, and 12) | *Phantom* limb pain intensity will be significantly decreased relative to baseline pain at various time points following a cryoneurolysis procedure (as measured by the Numeric Rating Scale within the Brief Pain Inventory). | Pain negatively influences physical and emotional functioning. |
| To estimate the analgesic effect of cryoneurolysis on intractable post-amputation (trans-femoral) *residual* limb pain at various time points post-treatment (Days 1, 7, and Months 1, 2, 3, 4, and 12) | *Residual* limb pain intensity will be significantly decreased relative to baseline pain at various time points following a cryoneurolysis procedure (as measured by the Numeric Rating Scale within the Brief Pain Inventory). | Pain negatively influences physical and emotional functioning. |
| To estimate the effect of cryoneurolysis on the *perception of well-being* in patients with intractable post-amputation (trans-femoral) phantom limb pain | The *perception of well-being* as measured with the Patient Global Impression of Change Scale will be improved at various time points following a cryoneurolysis procedure (Days 1, 7, and Months 1, 2, 3, 4, and 12) | Global perception of well-being is indicative of patients' own perception of their life status. |
| To estimate the effect of cryoneurolysis on the *physical and emotional functioning* of patients with intractable post-amputation (trans-femoral) phantom limb pain | The *physical and emotional functioning* of patients will be improved at various time points following a cryoneurolysis procedure relative to baseline as measured with the Brief Pain Inventory Interference Subscale(Days 1, 7, and Months 1, 2, 3, 4, and 12) | Pain negatively influences physical and emotional functioning. |
| **Tertiary/Exploratory** | | |

| OBJECTIVES | ENDPOINTS | JUSTIFICATION FOR ENDPOINTS |
|---|---|---|
| To estimate the effect of cryoneurolysis on the *incidence* and *duration* of non-painful phantom sensations in patients with intractable post-amputation (trans-femoral) phantom limb pain | The *incidence* and *duration* of non-painful phantom sensations will be improved at various time points following a cryoneurolysis procedure (Days 1, 7, and Months 1, 2, 3, 4, and 12) | Even non-painful phantom sensations may negatively influence patient well-being. |
| To estimate the effect of cryoneurolysis on the *incidence* and *duration* of *phantom* limb pain in patients with intractable post-amputation (trans-femoral) pain | The *incidence* and *duration* of *phantom* limb pain will be improved at various time points following a cryoneurolysis procedure (Days 1, 7, and Months 1, 2, 3, 4, and 12) | Pain negatively influences physical and emotional functioning. |
| To estimate the effect of cryoneurolysis on the *incidence* and *duration* of *residual* limb pain in patients with intractable post-amputation (trans-femoral) pain | The *incidence* and *duration* of *residual* limb pain will be improved at various time points following a cryoneurolysis procedure (Days 1, 7, and Months 1, 2, 3, 4, and 12) | Pain negatively influences physical and emotional functioning. |

# 4 STUDY DESIGN

## 4.1 OVERALL DESIGN

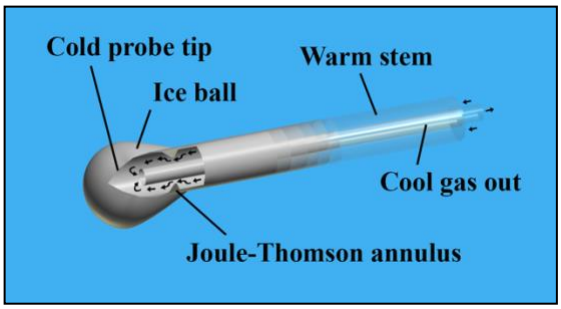
The study is a single-center, randomized, participant- and observer-masked, active-controlled, parallel-arm, optional crossover, human-subjects, post-market clinical pilot study to investigate the use of ultrasound-guided percutaneous cryoneurolysis to treat phantom limb pain following a trans-femoral (above-knee) amputation. Participants with intractable phantom limb pain will be randomly allocated to one of two possible treatments groups: cryoneurolysis (experimental) or sham (control). The primary outcome measure is the change in the phantom limb pain intensity from baseline 1 month following the procedure as measured by the Numeric Rating Scale within the Brief Pain Inventory.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Over 200,000 traumatic and surgical amputations occur annually within the United States alone; with an estimated 1.6-million people living with an amputation, and this number is expected to double by 2050. Among amputees, 35-98% (depending on the study) develop chronic, intractable pain perceived as being from the missing limb, a phenomenon termed “phantom limb pain”. The pain is usually described as “shooting, stabbing, boring, squeezing, throbbing, and burning”. 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 limb pain.

The exact reason that phantom limb pain occurs is unclear, but when a nerve is cut—as happens with an amputation—changes occur in the brain and spinal cord that increase with worsening phantom pain. These abnormal changes may often be corrected by putting local anesthetic—called a "nerve block"—on the injured nerve, effectively keeping any "bad signals" from reaching the brain with a simultaneous resolution of the phantom limb pain. However, when the nerve block resolves after a few hours, the phantom pain returns. But this demonstrates that the brain abnormalities—and phantom pain—that occur with an amputation are not necessarily fixed and may be dependent upon the "bad" signals being sent from the injured nerve(s). This, in turn, suggests that a very long peripheral nerve block—lasting many months rather than hours—may permanently reverse the abnormal changes in the brain and provide definitive relief from phantom pain. A prolonged nerve block lasting a few months may be provided by freezing the nerve using a process called "**cryoneurolysis**". **The ultimate objective of the proposed research study is to determine if cryoanalgesia is an effective treatment for intractable post-amputation phantom limb pain.**

**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". 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 cryoneurolysis devices (above right), the narrow-gauge probes (immediate right), and ultrasound[16,17] 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, the probe tip is frozen and subsequently withdrawn. **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 pain, including phantom limb 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 percutaneous cryoneurolysis procedure, nerve conduction is attenuated 2-3 months with the complete restoration of nerve structure and function following remyelination.

**There is currently no reliable treatment for phantom limb pain.** While more than 43 methods for treating phantom pain have been described, the placebo effect is common, and prolonged relief is experienced by fewer than 10% of treated patients (6% of untreated patients ultimately experience spontaneous resolution). Evidence of the intractable nature of phantom pain may be found in a survey of more than 10,000 amputees which reported a 1% treatment success rate. **Therefore, the overwhelming majority of people suffering from phantom limb pain are dependent upon opioid analgesics to gain even a small degree of relief.** There are few data from randomized trials to guide treatment, leading the authors of a major review to conclude that there remains a substantial "gap between research and practice in the area of phantom limb pain".

We have completed and published a Department of Defense-funded multicenter, randomized, double-masked, sham-controlled clinical trial investigating the use of ultrasound-guided percutaneous cryoneurolysis to treat existing post-amputation phantom limb pain (UCSD IRB 170973, now closed).[1] In short, patients who had a below-the-knee amputation (BKA) experienced prolonged benefit from active treatment (P=0.003); but patients who had an above-the-knee amputation (AKA) did not experience similar analgesia. Therefore, because the study was designed to analyze these two amputation levels together, the overall findings were negative (P=0.759). There is subsequently published evidence that the nitrous-oxide-based equipment that was used (PainBlocker, Epimed International, Dallas, TX) did not form a large or cold enough ice ball to adequately treat the larger nerves of the upper thigh for AKAs, resulting in a neuropraxia that worsened pain.[2] We theorize that the nitrous-oxide-based equipment that was used (PainBlocker, Epimed International, Dallas, TX) did not form a large or cold enough ice ball to adequately treat the larger nerves of the upper thigh for AKAs. In contrast, the ice ball size/temperature was adequate to treat the smaller nerves of the lower thigh for BKAs, resulting in cryoneurolysis and prolonged analgesia.

Given chronic pain's enormous costs to individuals and society—and the intractable, currently-untreatable nature of phantom limb pain with concurrent opioid dependence—it is imperative that an effective treatment be developed. If our study demonstrates that ultrasound-guided percutaneous cryoneurolysis is a successful treatment, the resulting impact on the hundreds-of-thousands of Americans suffering from intractable phantom limb pain will be **immediate and profound**, as (1) healthcare providers within the United States Armed Forces, Veterans Affairs Medical Centers, and civilian hospitals already have expertise placing ultrasound-guided peripheral nerve blocks; (2) cryoneurolysis is a relatively inexpensive, single-procedure, outpatient treatment with few complications; and (3) cryoanalgesia is already approved by the United States Food and Drug Administration.

### 4.3 JUSTIFICATION FOR DOSE

Not Applicable for this protocol which does not investigate a medication.

### 4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last follow up data collection time point (12 months) of the final enrolled participant.

## 5 STUDY POPULATION

A total of 20 individuals are anticipated for the analysis. However, to account for dropouts, will are requesting an additional 5 participants. This will total up to 25 participants.

### 5.1 INCLUSION CRITERIA

(1) Adult patients of at least 18 years of age
(2) Trans-femoral traumatic or surgical amputation at least 12 weeks prior to enrollment distal to the hip (femoral head remaining)
(3) Experiencing at least moderate phantom limb pain—defined as a 4 or higher on the Numeric Rating Scale (NRS; 0-10, 0= no pain; 10=worst imaginable pain)—at least daily for the previous 2 months
(4) Willing to avoid both changes to their analgesic regimen as well as elective surgical procedures from 1 month prior to and at least 4 months following the initial cryoneurolysis procedure

### 5.2 EXCLUSION CRITERIA

(1) allergy to amide local anesthetics
(2) pregnancy
(3) incarceration
(4) inability to communicate with the investigators
(5) morbid obesity (body mass index > 40 $kg/m^2$)
(6) possessing any contraindication specific to cryoneurolysis such as a localized infection at the treatment site, cryoglobulinemia, cold urticaria and Reynaud's syndrome

### 5.3 LIFESTYLE CONSIDERATIONS

NOT APPLICABLE.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

# 6 STUDY INTERVENTION

## 6.1 STUDY INTERVENTION(S) ADMINISTRATION

### 6.1.1 STUDY INTERVENTION DESCRIPTION

For individuals of childbearing potential, a sample of urine will be collected before any study interventions to confirm a non-pregnant state.
**Treatment group allocation (randomization).** Participants will be allocated to one of two possible treatments groups:

1. ***Cryoneurolysis***
2. ***Sham procedure (Control)***

Randomization lists will be created using computer-generated tables by the Investigational Pharmacy (UC San Diego) in a 1:1 ratio and block sizes of 2. Treatment group assignment will be conveyed to the investigators in the form of sealed, opaque envelopes only by the treating investigator. Therefore, all investigators and participants will be masked to treatment group assignment, with the only exception being the investigator who performs the procedure (and will not have subsequent contact with the participant). ***This protocol will enable a randomized, observer- and participant-masked, sham/placebo-controlled study.*** It is impossible to mask the individual performing the cryoneurolysis procedure because the ice ball forming at the distal end of the probe—with active treatment—is clearly visible by ultrasound; and the lack of an ice ball for placebo participants is equally clear. It is essential to continuously visualize the probe and target nerve throughout the two freeze/thaw cycles to ensure the entire nerve diameter is adequately treated and remains relatively motionless. This cannot be achieved if the ultrasound is turned off during nitrous oxide administration to mask the provider; and we prioritize patient safety over masking of the physician administering the intervention.
All participants will have a peripheral intravenous (IV) catheter inserted, standard noninvasive monitors applied (blood pressure cuff, pulse oximeter, 5-lead ECG), and oxygen administered *via* a nasal cannula or facemask. Midazolam and fentanyl (IV) will be titrated for patient comfort, while ensuring that patients remain responsive to verbal cues.

The cryoneurolysis sites will be cleansed with chlorhexidine gluconate and isopropyl alcohol. ***The nerves treated will include the femoral, sciatic, obturator, and lateral femoral cutaneous***. Each nerve will be visualized using ultrasound, a skin wheal of local anesthetic will be raised inferior to the transducer to anesthetize the skin and then the track towards the target nerve. The probe will then be inserted adjacent to the target nerve. The cryoneurolysis machine (CryoCare, Varian Medical Systems, Palo Alto, California) uses argon for the freeze cycle and helium to help decrease the thaw period duration. The cryoneurolysis device will be triggered using 1 cycle of 5.5-minute argon activation (2000-2500 PSI and 100% power) followed by a 30-second helium defrost. The Varian machine provides its own timer so that the gas cycle timing is precise to the second. This may be repeated, as necessary, to ensure the entire cross-section of each nerve is fully treated.

**Active Cryoneurolysis.** For participants randomized to active treatment, the probe placed in the patient will be triggered and the argon (and helium) passed through the probe and then back into the machine, and finally vented out from the console. This will result in a freeze-thaw cycle.

**Control.** For participants randomized to sham treatment, the probe in the patient will simply not be activated; instead, a second probe that is not inserted in the patient will be triggered which will create the same visual and auditory cues as for the active participants retaining the masked feature. The investigator administering the study intervention will activate the correct probe depending on the treatment group assignment. Therefore, all investigators and participants will be masked to treatment group assignment, with the only exception being the unmasked investigator who performs the procedure (and will not have subsequent contact with the participant).

It is impossible to mask the individual performing the cryoneurolysis procedure because the ice ball forming at the distal end of the probe—with active treatment—is clearly visible by ultrasound; and the lack of an ice ball for sham participants is equally clear. It is essential to continuously visualize the probe and target nerve throughout the freeze/thaw cycle(s) to ensure the entire nerve diameter is adequately treated and remains relatively motionless. This cannot be achieved if the ultrasound is turned off during nitrous oxide or argon administration to mask the provider; and we prioritize patient safety over masking of the physician administering the intervention.

Prior to discharge, subjects will be provided with verbal and written instructions, the telephone and pager numbers of an investigator, and a copy of the Institutional Review Board-approved consent form. The approximate duration of this visit will total 4 hours, from the time the subject enters the treatment facility until the time the depart.

**Optional crossover treatment.** Four to six months following the initial treatment, subjects ***may*** return for an optional repeated intervention procedure ("crossover") with the alternative treatment (either active cryoneurolysis or sham/placebo), again in a double-masked fashion using the same protocol as described for the initial intervention. **The crossover treatment is <u>not</u> required for study participation, as the primary analyses will include a parallel study design for the initial intervention evaluated prior to any crossover treatment.** However, an optional crossover treatment will be offered to subjects for two reasons: (1) it will ensure that all subjects have access to the proposed treatment, regardless of the treatment they are initially randomized to; and (2) it will permit intra-subject differences between treatments to be analyzed (e.g., assessing treatment-effect heterogeneity, or the variability of the causal effect across individuals, which will would not be available from the parallel-group portion of the study alone). These intra-subject differences will be secondary analyses, as there may be patient-selection bias regarding which subjects decide to have the crossover treatment (e.g., if the intervention is successful at greatly reducing phantom limb pain, then subjects receiving active cryoneurolysis during their initial treatment will be more likely to forgo the crossover treatment). This crossover will ***not*** affect the primary analyses, which will involve a parallel group study design and investigate the effects of cryoneurolysis within 4 months of the initial intervention. The approximate duration of a crossover visit will total 4 hours, from the time the subject enters the treatment facility until the time the depart. Following study completion, the results will be provided to all enrolled subjects using non-technical (i.e. "layperson") language, along with their treatment group assignment at the participants' request.

Following study completion, the results will be mailed electronically or by the United States Postal Service to all enrolled participants in written form using non-technical (e.g., "layperson") language.

### 6.1.2 DOSING AND ADMINISTRATION

Dosing is not applicable to this trial involving the investigation of a medical device, as opposed to a medication. Administration is described above in 6.1.1.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

The machines and the probes for cryoneurolysis will be stored in a locked office or workroom.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING.

Not applicable to this trial involving the investigation of a medical device, as opposed to a medication.

### 6.2.3 PRODUCT STORAGE AND STABILITY

The machines and the probes for cryoneurolysis will be stored in a locked office or workroom.

### 6.2.4 PREPARATION

Sterile probes will be used for the study intervention—they do not need “preparation”.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

These protocols will use a randomized, observer- and participant-masked, sham/placebo-controlled protocol. It is impossible to mask the individual performing the cryoneurolysis procedure because the ice ball forming at the distal end of the probe—with active treatment—is clearly visible by ultrasound; and the lack of an ice ball for sham participants is equally clear. It is essential to continuously visualize the probe and target nerve throughout the freeze/thaw cycle(s) to ensure the entire nerve diameter is adequately treated and remains relatively motionless. This cannot be achieved if the ultrasound is turned off during nitrous oxide or argon administration to mask the provider; and we prioritize patient safety over masking of the physician administering the intervention. Of note, given that this is a pilot study to help plan for a future trial, unmasking of treatment group assignment may occur following the primary outcome measure exclusively for the Principal Investigator if he feels it will assist in protocol development or requires the data for a future grant proposal.

## 6.4 STUDY INTERVENTION COMPLIANCE

Not applicable.

## 6.5 CONCOMITANT THERAPY

Not applicable.

### 6.5.1 RESCUE MEDICINE

During the procedure we will administer intravenous midazolam and fentanyl. Following the procedure we will not require changes to patients' current medication regimen, and we will not be providing prescriptions for analgesics as well—patients will continue to be under the care of their pre-existing pain physician (or primary care physician).

# 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 DISCONTINUATION OF STUDY INTERVENTION

Cryoneurolysis procedure will be discontinued if the participant requests during the procedure. Additionally, if the investigator feels that continuing with the intervention would adversely affect the patient's health—such as a hemorrhage—the intervention might be discontinued.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

**DISCONTINUATION CRITERIA**

1. Patients may withdraw voluntarily from participation in the study at any time and for any reason.
2. Patients may be withdrawn on the basis of the Investigator's clinical judgment, protocol deviation or loss to follow-up.
3. This study may be terminated at the discretion of any regulatory agency for reasons including safety and/or efficacy.
4. The Investigator (Dr. Ilfeld and site directors) may elect to discontinue or stop the study at his or her site for any reason including safety.
5. When a participant withdraws or is withdrawn before completing the study, the date and reason for withdrawal are to be documented in the CRF.

6. In the event that a patient is withdrawn prematurely due to an AE or serious AE, the AE or serious AE will be followed until it resolves or stabilizes, or until it is judged by the Site Investigator to be no longer clinically significant.

### 7.3 LOST TO FOLLOW-UP

Study participants may miss data collection phone calls—it is common even though the investigators attempt multiple contacts with participants at specified times—but this study will not consider any patient "lost to follow-up". We may not be able to collect all data for all participants at all study time points; but we will continue to attempt to contact participants until 12 months has passed for that participant (the duration of study participation) or the participant requests study withdrawal (in which case it is a withdrawal and not "lost to follow-up".

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

**Outcome measurements.** We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for chronic pain clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement. ***The primary end point will be the difference in average daily phantom pain intensity at baseline and 1 month following the initial intervention*** *(measured with the NRS as part of the Brief Pain Inventory).* The primary analyses will compare the two treatments (inter-subject comparisons) during the initial treatment period in which half of the subjects will receive active cryoneurolysis and the other half a sham/placebo treatment. Endpoints will be evaluated at baseline and post-treatment (Day 0), Days 1 and 7; and Months 1, 2, 3, 4, and 12, (Table 1). These same time points through month 4 will be evaluated following the optional second (crossover) treatment.

The questionnaire will differentiate among multiple dimensions of limb pain:

***Residual limb ("stump") pain:*** painful sensations localized to the portion of limb still present.
***Phantom limb sensations:*** *non*-painful sensations referred to the lost body part.
***Phantom limb pain:*** painful sensations referred to the lost body part.

Each type of pain/sensation will be defined for subjects immediately prior to questionnaire application at each time point, and subjects will be instructed to specifically address phantom limb pain when responding to the various questions. In addition, since there is a strong correlation between phantom and residual limb pain, we will specifically inquire about both types of pain. Each time the questionnaire is applied, subjects will be instructed to respond for the previous 3 days (e.g., worst pain during the previous 3 days) because studies have suggested that patients have "increasing difficulty actually remembering symptom levels beyond the past several days." Exceptions will be on Day 1 for both the initial and crossover treatments because at these time points, the interest is in subjects' experiences subsequent to the treatment and not prior to the intervention. During these two days, subjects will be instructed to respond for the period of time since their treatment.

**Table 1. Summary of post-enrollment assessments.**

| **Subjects:** | **All** | | | | | | | **Participating in Crossover *** | | | | | | | **All** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Time Point Following:** | **Initial** Treatment | | | | | | | **Crossover** Treatment | | | | | | | **Initial** |
| **Time Point (Days):** | 0 | 1 | 7 | | | | | 0 | 1 | 7 | | | | | |
| **Time Point (Months):** | | | | 1 | 2 | 3 | 4 | | | | 1 | 2 | 3 | 4 | 12 |
| Phantom Limb Pain (worst, least, average, current), NRS | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Residual Limb Pain (worst, least, average, current), NRS | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Patient Global Impression of Change Scale | | • | • | • | • | • | • | | • | • | • | • | • | • | • |
| Brief Pain Inventory Interference Scale | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Non-Painful Phantom Sensations (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Phantom Limb Pain (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Residual Limb Pain (# and duration) | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |

* The "crossover" treatment intervention will occur 4-6 months following the initial treatment

**Demographic and amputation history.** Subjects will have demographic and anthropomorphic data collected including age, sex, gender, height, weight, years of educational, employment status, marital status, military status, race, ethnicity, current analgesic regimen (including adjuvants such as acupuncture), comorbidities, and any chronic pain other than study limb including location and details. In addition, amputation-specific data will include side of amputation, anatomic location of amputation, contralateral amputation, years since initial amputation, time since phantom pain began, phantom pain description, time since residual pain began, date(s) of subsequent surgical procedures, amputation etiology, amputation level, other amputations (with dates/etiology/pain), and prosthesis use. Immediately prior to premedication the phantom and residual limb pain intensities will be record. Immediately prior to and then following the treatment of each peripheral nerve we will collect the phantom pain score, residual pain score, the treatment point from distal end of limb, duration of argon treatment, and the highest pain during the treatment. We will also note and describe any protocol deviations and adverse events.

All remaining data collection following the day of the intervention (Day 0) will be collected by telephone from the University of California San Diego by the investigators, Program Manager, and/or research coordinators specifically trained in these instruments' application, minimizing inter-rater discordance

and standardizing responses across all enrolling centers. Staff masked to treatment group assignment will perform all assessments. Each data collection phone call will require approximately 5 minutes.

***Hypothesis 1:*** Phantom limb pain ***intensity*** will be decreased relative to baseline 1 month following a cryoneurolysis procedure (as measured by the Numeric Rating Scale within the Brief Pain Inventory).

Current/present, worst, least, and average phantom pain will be assessed using a Numeric Rating Scale (NRS) as part of the Brief Pain Inventory (short form), with the "average" pain score designated as the primary endpoint. In addition, average and worst residual limb pain NRS will be recorded separately from the phantom pain scores. The NRS is a highly-sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain. The NRS has been demonstrated to be a valid and reliable measure in multiple pain states—including painful peripheral neuropathy specifically—and following analgesic interventions. In addition, NRS scores correlate well with other measures of pain intensity, and demonstrate high test-retest reliability in chronic nociceptive and neuropathic pain states. These NRS characteristics led to recent IMMPACT consensus recommendations for use of the 10-point NRS of pain intensity for chronic pain trials.

***Hypothesis 2a:*** Perception of **well-being** will be improved 1 month following one cryoneurolysis procedure (as measured with the Patient Global Impression of Change Scale).

While single-item measures of pain level/relief are currently the most reliable and valid options to measure pain intensity, the multidimensional aspect of the pain experience has led consensus recommendations for use of "global" measures of improvement in chronic pain trials. The Patient Global Impression of Change Scale is one such measure allowing patient evaluation of integrated treatment effects. This measure is a 7-point ordinal scale requiring the subject to rate the current severity of their global situation as it relates to phantom limb pain (as defined by each individual) compared to their baseline. This scale has the words "very much worse" to the left by the number one, and "very much improved" to the right, adjacent to the number seven. The words "no change" are in the middle of the scale above the number four. The Patient Global Impression of Change Scale has been validated in over ten prospective trials, including studies specifically involving peripheral neuropathy.

***Hypothesis 2b:*** Physical and emotional **functioning** will be improved relative to baseline 1 month following one cryoneurolysis procedure (as measured with the Interference Subscale of the Brief Pain Inventory).

It is well-recognized that, “pain is a complex, multidimensional, sensory, and emotional experience that is individually perceived and described in many different ways.” This observation has led to consensus recommendations that “multiple core domains and related measures be considered in pain treatment trials,” that “tap into a wider experience of pain over time and its impact on functioning and quality of life.” Therefore, the proposed trial will include the Brief Pain Inventory, an instrument that includes—in addition to pain intensity scales—seven measures evaluating the pain’s interference with physical and emotional functioning, such as sleep, relations with others, and enjoyment of life. It is this 7-question Interference Scale that will be used specifically for Hypothesis 2b. The Brief Pain Inventory has been used in countless clinical studies of chronic pain, and validated specifically in neuropathic pain states. This instrument is associated with minimal subject burden and is easily interpreted by patients of all ages and education levels. It has high test-retest reliability and correlates well with much longer questionnaires, including the McGill measures and EuroQol.

## 8.2 SAFETY AND OTHER ASSESSMENTS

Prospective subjects will be provided with informed consent and then screened for inclusion and exclusion criteria. The following safety and eligibility procedures will occur during that time:

- **Study Eligibility** – A study investigator will review all medical history, medications and the inclusion/exclusion criteria with the participants.
- **Informed Consent** - Participants will provide written informed consent prior to any other study procedures.
- **Vital Signs** – These include blood pressure, heart rate, temperature and respiratory rate as well as pulse oximetry and continuous 5-lead ECG.
- **Adverse Event Collection** – Patients’ progress notes will be followed during hospitalization and any adverse events recorded. Following discharge, investigators will inquire about any adverse or unexpected events that have occurred since the previous contact. All events will be evaluated by a study investigator and will be followed until resolution.

Any of the safety assessment results will be made available to participants should they request them.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

The FDA definition of an Adverse event is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An AE can be either (a) a new occurrence or (b) an existing process (including the disease under study) that increases significantly in intensity or frequency. The medical product may be a drug or a device, being used either prior to or after regulatory approval.

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An AE is **serious** when the patient outcome is one or more of the following:

- Death. Applies to the event that is the primary cause of death
- Life-threatening, meaning that the patient was at immediate or substantial risk of death from the event at the time that the event occurred. It does not include an event which hypothetically might have caused death if it occurred in a more severe form.
- Hospitalization, initial or prolonged, meaning that a hospital admission and/or prolongation of a hospital stay was required for the treatment of the AE, or occurred as a consequence of the event. It does not include a pre-planned elective hospital admission for treatment or diagnostic procedures, or, in general, a hospital admission of less than 24 hours duration.
- Disability or incapacity that substantially disrupts the patient's ability to carry out normal life functions and is persistent or significant.
- Congenital anomaly or birth defect.
- Important medical event that, although not immediately life-threatening, requires intervention in order to prevent one of the other serious outcomes listed above. Examples of such events are allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

#### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment.

The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

#### 8.3.3.3 EXPECTEDNESS

Brian Ilfeld, MD, study Principal Investigator (PI) will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described in the risk section for the study intervention.

### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during hospitalization or post-discharge follow-up data-collection phone calls.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

A study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

***Precautions and responses to possible specific adverse events:***

**Infection:** Cryoneurolysis will be placed under sterile conditions as is standard-of-care. In addition, all patients having mastectomy will receive perioperative antibiotics, which will further decrease any risk of infection. Should a treatment site become infected, the patient will have oral antibiotics prescribed.

**Bleeding:** Exclusion criteria include ongoing active anticoagulation and/or bleeding disorders to decrease the risk of bleeding. During application, vessels are avoided with the use of real-time ultrasound guidance. The investigators are all specifically trained and have experience using ultrasound guidance.

**Skin discoloration:** Discoloration only occurs if the ice ball encompasses the dermis and epidermis. For the current study, the target nerves will be 2-10 cm in depth with the ice ball radius approximately 0.5-1.0 cm (depending on thickness of treated nerve), so the ice ball will not be close to the epidermis. Using ultrasound guidance, the skin, muscles, and target nerves are easily imaged in real-time and avoiding the epidermis is a basic maneuver.

**Confidentiality:** 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.

### 8.3.5 ADVERSE EVENT REPORTING

A member of the study staff shall complete a summary report or log of all AEs and submit to the UCSD Office of IRB Administration at the time of study annual renewal or closeout.

### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

The study investigator shall complete an SAE Form and submit to the UCSD Office of IRB Administration as soon as possible, but no later than 10 working days after the investigator first learns of the effect.

### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

In the event of an SAE determined to be related to study procedure, participants will be informed after IRB review of the event. Upon IRB acknowledgement and study team fulfillment of any protocol changes, participants will be informed via a consent form addendum or a new version of the consent form. Participants will be given the choice to withdraw from the study or sign the new consent and continue.

### 8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

### 8.3.9 REPORTING OF PREGNANCY

Pregnancy is not considered an AE for this study: there is no prohibition against pregnancy following cryoneurolysis and study participants will not be counselled regarding subsequent birth control.

## 8.4 UNANTICIPATED PROBLEMS

### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to UCSD Office of IRB Administration. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 30 days of the investigator becoming aware of the problem.
- All unanticipated events and adverse events will be reported to the specific center's Institutional Review Board (IRB), the primary supervising IRB (University of California San Diego), the study Data and Safety Monitoring Board (DSMB), and the Army Human Research Protections Office. The adverse event and unanticipated event profile will be discussed at monthly executive committee video-conference meetings.

### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

In the event of a UP determined to be related to study procedure, participants will be informed after IRB review of the event. Upon IRB acknowledgement and study team fulfillment of any protocol changes, participants will be informed via a consent form addendum or a new version of the consent form. Participants will be given the choice to withdraw from the study or sign the new consent and continue.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 STATISTICAL HYPOTHESES

**Statistical analysis:** Continuous, normally distributed data will be reported as mean ± standard deviation. Nonparametric continuous or categorical data will be reported as median [10th-90th percentiles] or percent, as appropriate. Comparisons of independent samples will be performed using Student's t-test for parametric continuous variables or Mann-Whitney U test for nonparametric or categorical variables. The Chi Square test and Fisher's Exact test will be used for differences in proportions, as appropriate. $P<0.05$ will be considered statistically significant for the primary outcome. Results of comparisons in secondary outcomes will be interpreted as suggestive, requiring confirmation in a future trial before considering them as definitive.

## 9.2 SAMPLE SIZE DETERMINATION

This is a pilot study to assist in powering a subsequent definitive trial and we therefore use a convenience sample of 20 participants.

## 9.3 POPULATIONS FOR ANALYSES

A total of 20 individuals are anticipated for the analysis. However, will are requesting an additional 5 permitted to account for dropouts. This will total up to 25 participants.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

Please see above.

### 9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Please see above.

### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Please see above and as follows.

### 9.4.4 SAFETY ANALYSES

**Complications.** The investigators will record all related complications (all are extraordinarily rare). These complications cannot be "ranked", but rather the two groups will be compared descriptively on each of these possible complications.

### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

Balance on baseline covariates will be assessed using absolute standardized difference (ASD)175 i.e., difference in means or proportions divided by the standard deviation. ASD > 0.1 will be considered to indicate imbalance, and these variables will be adjusted for in the statistical analyses. Analyses will be carried out using modified intention-to-treat i.e., patients who received any study treatment will be analyzed according to the group they were randomized to.

### 9.4.6 PLANNED INTERIM ANALYSES

None.

### 9.4.7 SUB-GROUP ANALYSES

None.

### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual patient data will not be reported, only aggregate.

### 9.4.9 EXPLORATORY ANALYSES

This is a pilot study and therefore all of the analyses will be exploratory requiring confirmation in a subsequent adequately-powered clinical trial.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

### 10.1.1 INFORMED CONSENT PROCESS

**Enrollment.** Study subjects will be identified from 3 sources:

1. **Clinics.** The investigation team will meet with clinic (amputee-specific, surgical, and chronic pain) personnel to both in-service them on the study protocol as well as provide Institutional Review Board-approved written information describing the investigation that may be given to prospective subjects during clinic visits. Clinic patients will come into contact with their healthcare providers during regularly scheduled clinic visits, and these providers will briefly describe the study and offer written information to patients with phantom limb pain who voice interest in the study. Patients who are interested in the study will be required to give permission for a research coordinator to contact them to adhere to Health Insurance Portability and Accountability Act (HIPAA) requirements.

2. **Advertisements.** The Primary Investigator will place Institutional Review Board-approved study advertisements within print and web-based publications that are frequently read by the target population. Additionally, we will provide similar Institutional Review Board-approved advertising material to the leaders of local and regional amputee focus/support groups. Individuals who are interested in the study will be directed to contact the study investigators or research coordinators for a thorough description of the study purpose and protocol. In addition, Institutional Review Board-approved advertisements will be placed, and a study-specific information page created within Facebook, which has over 1-billion members. Of note, the United States Army, Navy, Air Force, and Marines all have dedicated Facebook information pages. Information on how to volunteer for the study will also be placed in relevant Twitter (now “X”) feeds, such as the Clinical Trial Spotlight San Diego, and Clinical Connection, free portals for finding clinical trials.

3. **ClinicalTrials.gov.** The trial will be prospectively registered on the ClinicalTrials.gov website. One of the main purposes of trial registries is to provide the general population access to available ongoing

investigations. Contact information for the site directors will be included on the website so that prospective subjects may receive a thorough description of the study purpose and protocol.

Once a prospective subject contacts an investigator or research coordinator by telephone or email, they will be provided information on the study purpose and protocol, as well as have any questions answered. Inclusion/exclusion criteria will be reviewed and documented on a form to identify subject eligibility according to these criteria. If a prospective subject is excluded for any reason, the reason for exclusion will be recorded, but no patient identifying information will be recorded. Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled for their initial study treatment. Written informed consent will be attained prior to any measurements or procedures prior to the initial treatment (see below for a detailed description of the informed consent process).

We are requesting a partial waiver of HIPAA authorization for recruitment as protected health information will be reviewed to ascertain appropriate inclusion/exclusion criteria:

1. These procedures are minimal risk to the potential participants as we are asking focused medical questions (e.g., where is your amputation?) and are not recording the responses—they are used to simply ascertain whether or not the prospective participant meets criteria.

2. A waiver of HIPAA authorization for recruitment would not adversely affect the rights and welfare of the potential participants as we are asking focused medical questions (e.g., where is your amputation?) and are not recording the responses—they are used to simply ascertain whether or not the prospective participant meets criteria.

3. This clinical trial could not be practicably carried out without the waiver because we must ascertain inclusion/exclusion criteria before the prospective patient has travelled to the medical center. If they meet criteria, then they can decide whether or not to schedule the intervention; and we will collect written, informed consent as documented with an IRB-approved ICF at the beginning of their visit and prior to any questionnaires or procedures.

4. After prospective 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 for recruitment to be granted:

1. Identifiers will include the potential participant's age, level of amputation, pain levels, and willingness to avoid both changes to their analgesic regimen as well as elective surgical procedures from 1 month prior to and at least 4 months following the initial cryoneurolysis procedure. In addition, we will inquire about any allergy to amide local anesthetics, pregnancy, incarceration, ability to read English (for the ICF), weight and contraindications specific to cryoneurolysis such as a localized infection at the treatment site or Reynaud's syndrome. This information will not need to be recorded in hard-copy format. If the patient does not participate, then there will be no record of PHI specifically for study

purposes whatsoever. If the patient does participate, then PHI will be recollected following written, informed consent.

2. This clinical trial could not be practicably carried out without the waiver because we must ascertain inclusion/exclusion criteria before the prospective patient has travelled to the medical center. If they meet criteria, then they can decide whether or not to schedule the intervention; and we will collect written, informed consent as documented with an IRB-approved ICF at the beginning of their visit and prior to any questionnaires or procedures.

3. The privacy risk to individuals whose PHI will be used is minimal since we will not record any PHI specifically for study purposes until after written, informed consent is provided. The anticipated benefit to participants is a chance of improving their pain control if they are randomized to active treatment.

4. PHI that will be evaluated includes the items listed in #1 above.

An investigator or research coordinator will review the study protocol in detail with interested prospective participants; and, for patients desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or interventions. The method of documenting informed, written consent will be IRB-approved consent forms. Vulnerable populations will not be enrolled.

Once a prospective participant contacts (or gives permission to be contacted by) an investigator or research coordinator, 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 provided with written informed consent prior to any measurements or procedures prior to the intervention. The Principal Investigator is responsible for ensuring that written, informed consent is obtained from every participant. Clinical research coordinators will be specifically trained by the Principal Investigator to provide informed consent followed by documentation of informed consent using an Institutional Review Board-approved informed consent form. This will occur in private patient care areas, so that participants may feel comfortable asking questions.

We do not foresee any issues relevant to the mental capacity of the potential 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 the site director or research coordinator, as described above; and also the day 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.

Surrogate consent will not be accepted; therefore, if patients cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative will be unacceptable for study enrollment.

If a protocol amendment is required, then the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the UCSD Human Research

Protections Program and signed by all participants subsequently enrolled in the clinical study, as well as those currently enrolled in the clinical study as applicable.

### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause by either the Principal Investigator or the IRB. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely suspended or terminated, the Principal Investigator will promptly inform the Institutional Review Board and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of any changes to the data collection schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy or futility that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the PI and IRB.

### 10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policy requirements.

All case report forms (data capture forms, or "CRFs") will be identified by only the randomization number and first and last initials of the participants' names (as a check for the randomization numbers). Therefore, any protected health information will be separated from identifiers. The connection

between participant identifiers and the randomization numbers will be accessible solely by the Principal Investigator and Program Manager (for follow-up data collection purposes). Therefore, no case report form will be tied to an identifiable individual on the forms themselves, ensuring patient confidentiality should a form be inappropriately accessed. All case report forms will be retained in the locked offices of the Principal Investigator and/or Program Manager. These hard copies will not be mailed or otherwise transferred and will remain available to audit for a minimum of 7 years. The IRB is eligible to review study records at any time.

### 10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

The original, hard copy signed informed consent forms and case report forms will be stored within the Principal Investigator and/or Program Manager'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.

### 10.1.5 KEY ROLES AND STUDY GOVERNANCE

| **Principal Investigator** |
|---|
| Brian M. Ilfeld, MD,MS |
| University of California, San Diego |
| 9452 Medical Center Drive<br>La Jolla, CA 92037 |
| (858) 444-5949 |
| bilfeld@health.ucsd.edu |

### 10.1.6 SAFETY OVERSIGHT

The study oversight will be the purview of the Principal Investigator; but all investigators, the Program Manager, and research coordinators have the obligation to report any safety issues/violation to the Principal Investigator.

### 10.1.7 CLINICAL MONITORING

This is an investigator-initiated clinical trial so there will be no formal monitoring of the study. However, all study staff have training and extensive experience working on investigator-initiated studies and will ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently

approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

## 10.1.8 DATA HANDLING AND RECORD KEEPING

### 10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The investigators will create a hard-copy case report form for each study participant enrolled, which will include only the randomization number and first/last name initials (as a check), anthropometric (e.g., age, height, weight), and demographic information. All case report forms will be identified by only the randomization number and first and last initial of the participants' names (as a check for the randomization numbers). Therefore, any protected health information will be separated from identifiers. The connection between participant identifiers and the randomization numbers will be accessible solely by the Principal Investigator and Program Manager (for follow-up data collection purposes). Therefore, no case report form will be tied to an identifiable individual on the forms themselves, ensuring patient confidentiality should a form be inappropriately accessed. All enrollment and case report forms will be retained in the locked offices of the Principal Investigator and/or Program Manager. The data from each enrollment form will be uploaded to the project database. These hard copies will not be mailed or otherwise transferred and will remain available to audit for a minimum of 7 years.

### 10.1.8.2 STUDY RECORDS RETENTION

The data from each enrollment form will be uploaded to the project database. These hard copies will not be mailed or otherwise transferred and will remain available to audit for a minimum of 7 years.

## 10.1.9 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the study investigator to use continuous vigilance to identify all deviations and report appropriate deviations (such as those related to an SAE) within 10 working days. All deviations

must be addressed in study source documents and ultimately reported to the UCSD Office of IRB Administration.

## 10.2 ADDITIONAL CONSIDERATIONS

### 10.2.1 ALTERNATIVES TO STUDY PARTICIPATION:

Potential study participants may simply decline enrollment.

### 10.2.2 EXPENSE TO PARTICIPANT:

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

### 10.2.3 COMPENSATION FOR PARTICIPATION:

To help compensate subjects for their time and to defray travel expenses, they will receive $750 following each visit for treatment, for up to $1500 for subjects who undergo both an initial treatment and crossover treatment. Currently, 24 USC 30 limits payments to Active Duty military personnel for participation in research while on duty to blood donations (which are not required for the proposed investigation). However, military personnel who are on official military leave status may receive compensation for study participation and will do so at the same level and on the same schedule as described for civilians and Veterans. Compensation will be provided to the subjects following the study treatment and before they go home in the form of an unrestricted debit card.

### 10.2.4 Management of adverse events:

Adverse events for study-related injuries will be managed by the Principal Investigator. For a medical emergency that is potentially life-threatening, participants will be instructed to dial 911 for emergency services to go directly to their location. In the event of a study-related injury, UC San Diego will provide medical care needed to treat those injuries without cost to study participants. UC San Diego will not provide any other form of compensation for study-related injuries. This information is specified within the informed consent forms. The forms also instruct participants to contact the UC San Diego Institutional Review Board or the Principal Investigator for further information (phone numbers provided for all entities).

### 10.2.5 PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES:

Principal Investigator, Brian M. Ilfeld, MD, MS, is a board-certified anesthesiologist with fellowship training in and 22 post-training years' experience with regional anesthesia, acute pain medicine, and clinical investigation. 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 participants following their treatment. Dr. Ilfeld will be responsible for the overall management of this study. Co-investigators, Rodney Gabriel, MD, John Finneran, MD, and Engy Said, MD, are board-certified 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 participants, perform a history and physical exam, perform the treatment on participants, and will follow participants following their treatment.

Baharin Abdullah is a Program Manager with the Department of Anesthesiology with the required experience and training—including up-to-date CITI training—for her position.

**10.2.6 FUNDING SUPPORT FOR THIS STUDY:** There is no extramural funding available for this trial, although the investigators will pursue such funding. Department funding will be used in the interim or if no extramural funding is award. Please contact Kimberly Giles, grants specialist, at kgiles@health.ucsd.edu for information regarding Departmental funding.

## 10.3 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ACTRI | Altman Clinical & Translational Research Institute |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| ICF | Informed Consent Form |
| IEC | Independent Ethics Committee |
| IRB | Institutional Review Board |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event |
| UCSD | University of California, San Diego |
| WHO | World Health Organization |

## 10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.*

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.1 | 21-oct-2023 | **"2000 PSI" has been revised to "2000-2500 PSI"** | **For the study, we will be treating multiple nerves as described in the plan, each of a different size, shape, and anatomic location. Therefore, we often have to use different probes (for example, one creates a round ice ball while another an oval-shaped ice ball), which require different pressures. So, "2000 PSI" has been revised to "2000-2500 PSI" in two different locations.** |
| 1.2 | 11-Dec-2023 | **Increase in subject compensation from $200 to $750.** | **We are increasing subject compensation from $200 to $750. We have participants from around the country who are interested in participating in the study, but participants can't afford to travel. We recently received the Senate grant, so now we can afford to increase the compensation.** |
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## 12 APPENDIX