Title: Treating Phantom Limb Pain Using Continuous Peripheral Nerve Blocks: A Department of Defense Funded Multicenter Study

NCT: NCT01824082

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

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

Version date: 05/11/2011

1. PROJECT TITLE

Treating Intractable Post-Amputation Phantom Limb Pain With Ambulatory Continuous Peripheral Nerve Blocks

2. PRINCIPAL INVESTIGATOR

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3. FACILITIES

The multicenter clinical trial will be implemented at geographically distributed U.S. military, Veterans Affairs, and civilian university medical centers:

U.S. military medical centers:

- Walter Reed National Military Medical Center, Bethesda, Maryland
- Naval Medical Center San Diego, San Diego, California

Veterans Affairs medical center:

- Palo Alto Veterans Affairs Medical Center, Palo Alto, California

Civilian university medical centers:

- University of California San Diego, San Diego, California
- Cleveland Clinic, Cleveland, Ohio

4. ESTIMATED DURATION OF THE STUDY

5 years

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

When a limb is traumatically severed (such as a car accident), pain perceived in the part of the body that no longer exists often develops. This is called "phantom limb" pain, and is different from "residual limb" or "stump" pain, which is pain in the part of the limb that remains intact. Unfortunately, phantom pain resolves in only 16% of afflicted individuals, with the rest experiencing this pain for the rest of the lives. There is currently no reliable treatment for phantom limb pain. The exact reason that phantom limb pain occurs is unclear, but when a nerve is cut—as happens with a traumatic amputation—changes occur in the brain and spinal cord that actually worsen with increasing phantom pain. These abnormal changes may often be corrected by putting local anesthetic—termed a "peripheral nerve block"—on the injured nerve, effectively keeping any "bad signals" from reaching the brain, and the phantom limb pain goes away also. However, when the nerve block wears off 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 permanent, and may be dependent on the "bad" signals being sent from the injured nerve(s). This suggests that a very long peripheral nerve block—lasting many days rather than hours—may permanently reverse the abnormal changes in the brain, and provide lasting relief from phantom pain**.** An option called a "continuous peripheral nerve block" is now available to keep the area numb for days rather than hours. This technique involves the placement of a tiny tube—smaller than a piece of spaghetti—through the skin and next to the nerves supplying the amputated limb. The purpose of this study is to determine if putting the numbing medication through one or two tiny tube(s) placed next to the nerve(s) that go to an amputated limb, for six days, will decrease phantom limb pain.

6. SPECIFIC AIMS

The ultimate objective of the proposed research is to determine if ambulatory CPNB is an effective treatment for intractable phantom limb pain following a traumatic limb amputation.

- Primary Specific Aim: To test the influence of a prolonged ambulatory perineural local anesthetic infusion (CPNB) as compared to placebo on the intensity of existing, intractable phantom limb pain resulting from a traumatic amputation.
  - Hypothesis 1: Phantom limb pain intensity will be significantly decreased 4 weeks following an ambulatory CPNB (as measured by the Numeric Rating Scale within the Brief Pain Inventory).
- Secondary Specific Aim: To test the influence of a prolonged ambulatory perineural local anesthetic infusion (CPNB) as compared to placebo on the quality of life for individuals with intractable phantom limb pain resulting from a traumatic amputation.
  - Hypothesis 2a: Perception of well-being will be significantly improved 4 weeks following an ambulatory CPNB (as measured with the Patient Global Impression of Change Scale).
  - Hypothesis 2b: Physical and emotional functioning will be significantly improved 4 weeks following ambulatory CPNB (as measured with the Brief Pain Inventory).
  - Hypothesis 2c: Depression will be significantly decreased 4 weeks following an ambulatory CPNB (as measured with the Beck Depression Inventory).

The proposed randomized, triple-masked, placebo-controlled clinical trial has a strong potential to identify the first reliably effective treatment for intractable phantom limb pain following a traumatic limb amputation.

7. BACKGROUND AND SIGNIFICANCE

As the explosive power of modern armaments continues to increase, far more tissue destruction occurs than in the past.[1,2] At the same time, multiple advances—from body armor to rapid evacuation to forward-deployed mobile operating rooms—have increased the survival rate to more than 90%.[3] The dramatic increase of improvised explosive devices in Afghanistan and Iraq have also led to a higher percentage of casualties suffering blast injuries to their limbs.[4,5] **The combination of increased munitions force, use of improvised explosive devices, and casualty survival rates has resulted in a dramatic increase in the percentage of injured combat veterans living with a traumatic amputation.**[4,6] From October 2001 through June 2006, over 70% (5,684) of U.S. military casualties involved major limb injuries.[7] Of these, 88% resulted from explosive devices and 469 had a limb amputation proximal to the wrist or ankle joint.[7] Furthermore, military amputees are generally younger and healthier (at baseline) than their civilian counterparts, and desire to continue either service within the U.S. Armed Forces or employment within the private sector. In the past decade, over 16% of U.S. forces suffering an amputation returned to active duty, compared with only 2% during the 1980s.[8]

Additionally, traumatic amputations have occurred in every major military conflict, leaving tens-of-thousands of United States Armed Forces Veterans with missing limbs. ***Of American Veteran amputees from World War II through the present, 35-98% (depending on the study) develop chronic, intractable pain perceived as being from the missing limb, a phenomenon termed "phantom limb pain"***.[9-11] The pain is usually described as "shooting, stabbing, boring, squeezing, throbbing, and burning".[9,12] **Phantom pain resolves in only 16% of afflicted individuals,**[13] leaving the rest to suffer for the remainder of their lives. Chronic pain greatly increases the risk of depression, while decreasing quality of life and the chances of return to duty or civilian work.[13,14]

There is currently no reliable treatment for phantom limb pain.[15] While more than 43 methods for treating

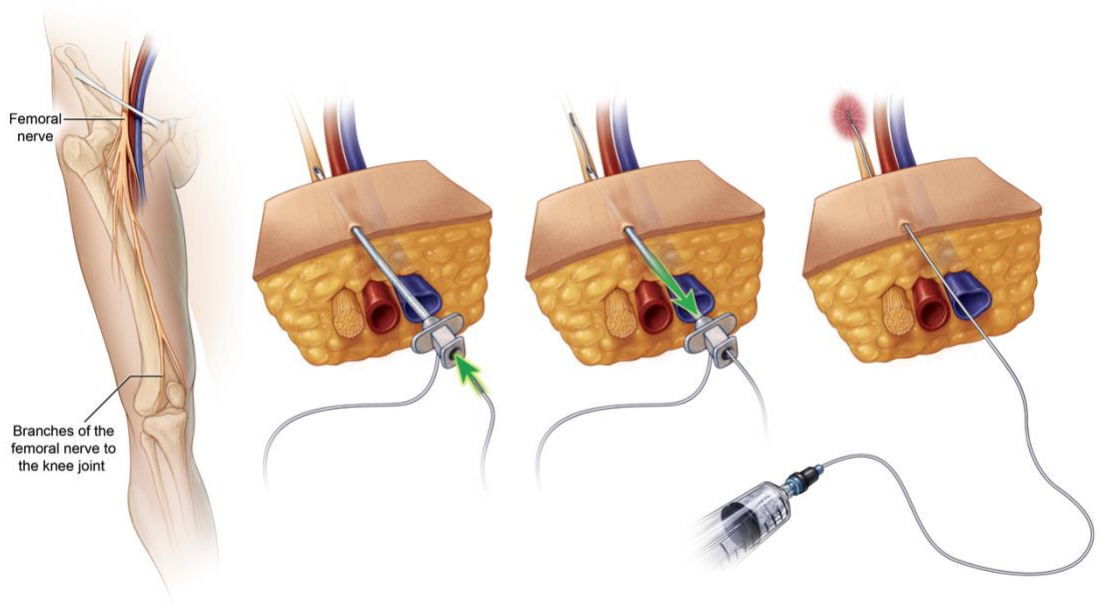
phantom pain have been described,[16,17] prolonged relief is experienced by fewer than 10% of treated patients (as well as 6% of untreated patients).[10] Evidence of the intractable nature of phantom pain may be found in a survey of more than 10,000 amputees who, remarkably, reported only a 1% success rate for treatment of phantom pain.[18] 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".[15] Developing a reliable treatment is difficult given the lack of understanding of the mechanism(s) and underlying pathophysiology resulting in phantom pain.

Current evidence suggests that when a nerve is severed—as occurs during a traumatic limb amputation—the barrage of nociceptive input triggers a complex interaction between the peripheral and central nervous system. Both systems are dynamic, and injury to peripheral nerves provokes changes in the spinal cord, thalamus, and cerebral cortex which are referred to as "neuronal plasticity".[19] Reorganization at the level of the spinal cord may result in "sensitization" in which responses to peripheral stimulation results in an exaggerated response, leading to stump allodynia and hyperalgesia.[20] Additionally, the somatosensory cortex, which "maps" somato-sensory inputs from the body—each location represented in a specific area of the cortex (i.e. homunculus), undergoes plastic changes of this map following deafferentation.[21] For example, the cortical zone representing the fingers may be invaded by adjacent areas following a hand amputation and consequent deafferentation.[22]

New imaging techniques such as functional magnetic resonance imaging have documented a correlation between phantom limb pain and cortical reorganization—with the most intense phantom pain provoking the greatest cortical changes.21 Amazingly, when the neural input from an amputated limb was blocked with a single injection of local anesthetic (a peripheral nerve block) in six patients, three had ***immediate, complete resolution of their phantom pain***; and, ***within minutes the cortical abnormalities were corrected for these three individuals***.[23] Unfortunately, when the single-injection nerve block resolved after a few hours, the phantom pain returned. But, this intriguing result demonstrates that the abnormal mapping—and phantom pain—that occur with amputation are not necessarily fixed, and may be dependent on signaling from the peripheral nervous system. Importantly, studies of chronic low back pain demonstrate that cortical thickness and cognitive abilities increased simultaneously 6 months after pain treatment.[24] These results demonstrate that chronic-pain-induced functional and structural brain abnormalities are not only reversible, but that treating chronic pain can restore normal brain function.[24] In other words, chronic phantom pain and cortical abnormalities may be maintained from abnormal peripheral input, suggesting that ***a peripheral nerve block of extended duration—lasting days rather than hours—may <u>permanently</u> reorganize cortical pain mapping, thus providing <u>lasting</u> relief from phantom pain.***

Continuous peripheral nerve blocks. Until recently, extending a peripheral nerve block beyond 16 hours was unrealistic. However, a relatively novel treatment option—"perineural local anesthetic infusion", or a **"<u>continuous peripheral nerve block</u>" (<u>CPNB</u>)**—is now available (Figure 1). This technique involves the percutaneous insertion of a catheter directly adjacent to the peripheral nerves supplying the affected limb. Local anesthetic is then infused *via* the catheter(s) inducing a completely insensate extremity for as long as desired without any systemic side effects.[25]

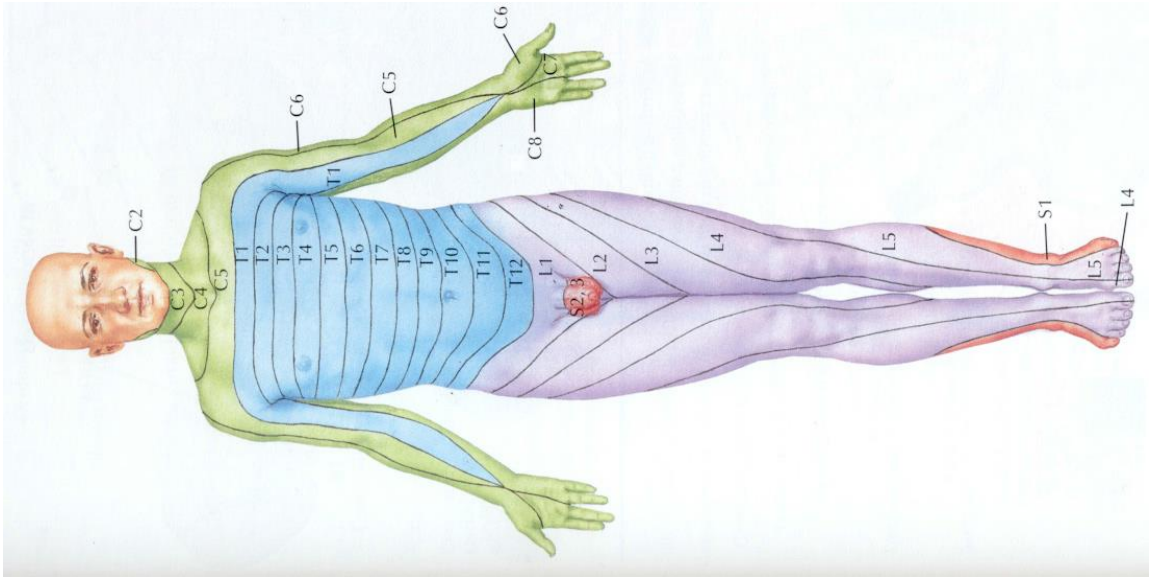
Figure 1. A continuous peripheral nerve block using a femoral perineural catheter.



Two case reports describe a total of three patients with phantom limb pain immediately following surgical amputation who were treated with multiple-day hospital-based CPNB. These patients experienced ***complete resolution of their phantom pain upon initiation of the CPNB, and no return of the phantom pain during the 7-12 month follow-up period***.[26] In an uncontrolled series of 19 patients also with phantom limb pain treated with hospital-based CPNB in the immediate post-amputation period, pain intensity decreased by approximately 50% at 1 and 6 months.[27] Therefore, there is great promise of treating phantom limb pain with CPNB. **However, no randomized, controlled trial has systematically investigated this possible intervention**. Reports to date include CPNB exclusively in the immediate post-amputation period, as opposed to applying CPNB in patients with temporally-remote amputations who already suffer from intractable phantom limb pain.

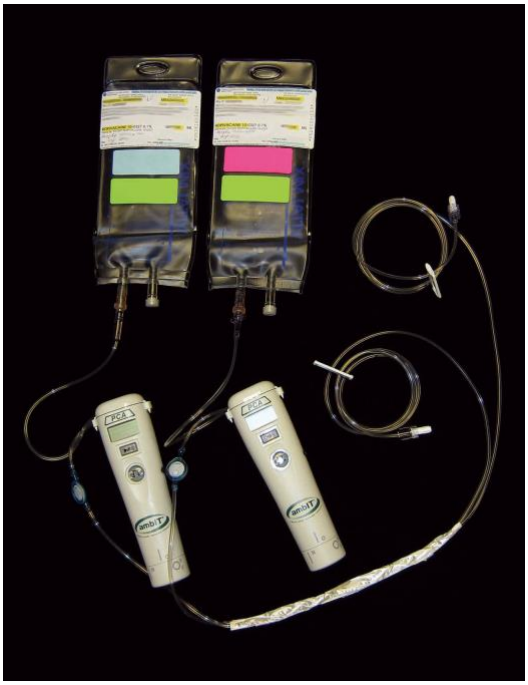
Ambulatory CPNB. There is limited evidence that for *surgical* amputations, a pre-emptive local anesthetic infusion *via* an epidural catheter may decrease the incidence of subsequent phantom limb pain.[28,29] Obviously, it is impossible to provide a preemptive intervention in cases of traumatic amputation. Further, treating chronic, intractable phantom pain with an epidural is problematic due to several significant limitations of this analgesic technique. Most importantly, epidural infusion may not be provided for upper extremity amputation; and, even when used for lower extremity amputation, the infusion affects both limbs equally since the local anesthetic effects distribute by dermatome rather than being restricted to individual peripheral nerves (Figure 2). Bilateral epidural effects require a low dose of local anesthetic to allow sensation in and ambulation using the uninjured limb; the consequence is inadequate analgesic effects in the amputated limb. Furthermore, epidural infusion often causes urinary retention and sympathectomy-induced postural hypotension;[30] epidural analgesia thus usually requires hospitalization for close monitoring and possible intervention. The high cost of prolonged hospitalization for epidural infusion is a strong deterrent for both research and practical application.

Figure 2. Human dermatomes.



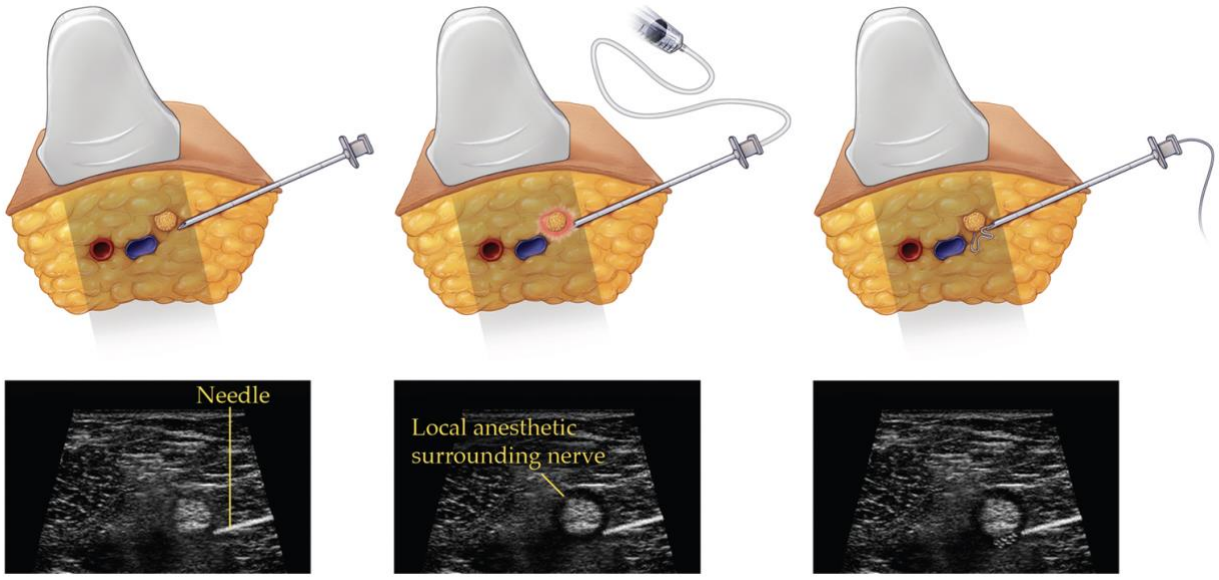
In contrast, CPNB affects only the target peripheral nerves. ***Therefore, CPNB may be provided for both upper and lower extremity trauma, has no undesirable side effects, and may be provided on an ambulatory basis using small, portable pumps to infuse the local anesthetic (Figure 3).***[31] No healthcare facility admission is required for perineural local anesthetic infusion, enabling individuals to remain in the comfort of their own homes without the expense of a prolonged hospitalization. Furthermore, at the end of the infusion individuals may easily remove the catheters themselves (or with a nonmedical caretaker) by simply removing the sterile dressing and gently pulling on the catheter.[32] Recent technological advances in electronic, programmable infusion pumps permit extraordinarily precise flow rates with an infusion duration of over a week in a very small, light, portable pump.[33-36] Ambulatory CPNB is no longer an "experimental" technique;[37] instead, it is an analgesic modality that is commonly used in all major military and civilian academic centers, as well as in countless private practices world-wide.[38] However, this technique has nearly exclusively been used to treat acute pain immediately following surgery rather than chronic pain states.[31]

Figure 3. Two portable, programmable, electronic infusion pumps used to administer local anesthetic to dual femoral and popliteal-sciatic catheters following below-knee amputations.



Ultrasound guidance. For over three decades, perineural catheters were inserted using electrical current to place an insulated needle adjacent to a peripheral nerve, followed by injection of local anesthetic and subsequent perineural catheter insertion.[39] While multiple prospective studies document the possible high success rate of this procedure in surgical patients with an intact limb,[39-42] an amputated limb usually precludes this technique since there is no hand/fingers or foot/toes to observe for electrically-induced movement (indicating close needle-nerve proximity).[43] Recently,[38,44-46] ultrasound-guidance has been used to image a target nerve, guide a percutaneously-inserted needle to that nerve, and ensure a perineural catheter inserted through the needle remains adjacent to the nerve following needle removal (Figure 4).[47] ***This new technique now enables accurate and reliable perineural catheter insertion in patients with an amputated limb***.[43]

Figure 4. Ultrasound-guided perineural catheter insertion for the sciatic nerve in the popliteal fossa (ultrasound images below illustrations).

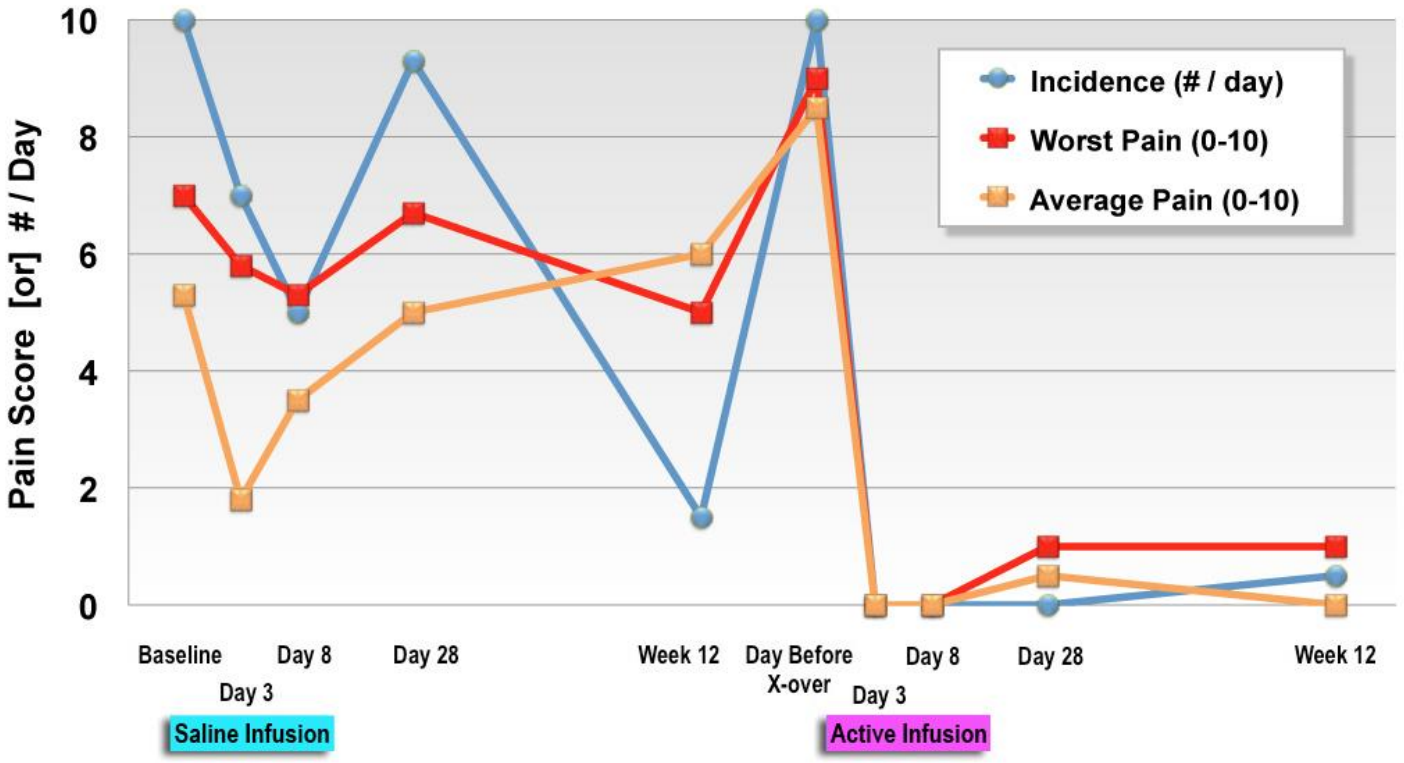


Preliminary data. We have completed a randomized, double-masked, placebo-controlled, crossover pilot study suggesting that a 6-day ambulatory CPNB may completely resolve previously intractable phantom limb pain. Three men, ages 25-47, with lower (2) or upper (1) extremity amputations and intractable phantom limb pain of at least 12 months duration were enrolled in this Institutional Review Board-approved pilot study. Written, informed consent was attained from each participant. Using ultrasound guidance,[43,47] perineural catheters were inserted on an outpatient basis: femoral and popliteal-sciatic for the two below-knee amputations, infraclavicular brachial plexus for the upper extremity amputation. Subjects were randomized to receive either a local anesthetic, ropivacaine (0.5%), or a normal saline placebo. Small, light-weight, portable, programmable, electronic infusion pumps administered the study solution at fixed rates, depending on catheter location: femoral 2 mL/h; popliteal-sciatic 5 mL/h; and infraclavicular 7 mL/h (Figure 3). With 1,000 mL pump reservoirs, subjects were provided with 6 days of perineural infusion in the comfort of their own homes. Subsequently, catheters were removed by the participants based on instructions given by telephone.[31] Data collection occurred by telephone on Days 3, 8, 28, and at 12 weeks after catheter insertion. Four months after the initial catheter insertion, subjects returned for repeated perineural catheter insertion ("crossover"), and received 6 days of ambulatory infusion with the alternate solution (either ropivacaine 0.5% or normal saline), again in a double-masked fashion.

By chance, all three subjects received placebo during their initial infusion, and none reported any change in their phantom limb pain. One subject with a below-knee amputation returned to active duty overseas prior to receiving his second infusion with active drug. However, the remaining two subjects reported ***complete resolution of their phantom limb pain during and immediately following treatment with ropivacaine (Figure 5).*** Within the 12-week follow-up period, one subject experienced no phantom pain recurrence; and the other subject reported mild pain occurring once each week of just a small fraction of his original pain (pre-treatment: continuous phantom pain rated 10/10; post-treatment: no phantom pain at baseline with average of 1 phantom pain each week rated 2/10). There were no local anesthetic side effects or adverse events in any of these subjects. In fact, six prospective studies of over 7,500 subjects all found that major CPNB complications are extraordinarily rare,[37] with fewer than 0.1% of individuals experiencing a major complication directly related to

CPNB.[48-53]

Figure 5. ***Pilot study results:*** **phantom limb pain intensity and daily incidence (mean values) prior to, during, and following both a saline and local anesthetic perineural infusion**



Relevance and applicability. Within the United States Armed Forces, the incidence of traumatic amputation is dramatically increasing due to the confluence of multiple factors, including increased munitions force, used of improvised explosive devices, and casualty survival rates.[4,6] From 2001-2006, over 70% of all U.S. military casualties endured a major limb injury,[7] with an amputation rate of 28% within Operation Enduring Freedom alone.[4] The United Nations estimates there are over 100 million land mines arrayed Worldwide, with over 10 million in Afghanistan alone (excluding improvised explosive devices).[4] The risks and incidence of traumatic amputation facing U.S. military service members is expected to remain high in the foreseeable future. And, while the amputation rate during the past decade of military action is at an all-time high (28%), previous conflicts (rate: 14-19%) have left tens-of-thousands of United States Armed Forces Veterans with missing limbs. ***Considering chronic, debilitating phantom limb pain develops in 35-98% of amputees (depending on the study),[9-11] currently has no reliable treatment,[15] and resolves in only 16% of those afflicted, this pathology is of major importance to the U.S. Armed Forces.***

In addition, over 200,000 traumatic and surgical amputations occur annually within the United States civilian population alone;[54] and over **1.6-million Americans** are currently living with an amputated limb.[55] Within the civilian population, the *lowest* published incidence of phantom pain from 16 different investigations ranges from 50-95%.[12,56,57] The economic toll for chronic nonmalignant pain is over $100-billion annually within the United States.[54] Given chronic pain's enormous costs to individuals, the United States military and government, as well as society as a whole—and the intractable, currently untreatable nature of phantom limb pain—it is imperative

that an effective treatment be developed.

Moreover, the optimal current treatment for phantom pain—systemic opioids—is associated with significant risks such as respiratory depression, cognitive impairment,[58] and addiction, especially in populations with co-existing psychopathology (e.g., combat stress, depression) common in wounded service members.[59] Evidence of the latter may be found in the most-recent (2009) Department of Defense Survey of Health Related Behaviors Among Active Duty Military Personnel Report.[60] Within the U.S. Armed Services, the most-commonly abused class of prescription drugs is opioids prescribed for chronic pain.[60] And, in the three years following 2002, the incidence of prescription drug misuse increased from 2% to 5%; and again more than doubled in the three following years, to 11%.[60] This alarming trend has not abated, and the Army has recently instituted a policy to limit opioid prescription use due to the rising rates of abuse.[61] **While not specific to phantom limb pain treatment, the Department of Defense has since prioritized non-addictive analgesic modalities for pain states that are currently treated primarily with prescription pain agents, such as opioids.** In addition, alternative treatments/adjuvants such as gabapentinoids and tricyclic antidepressants also have significant drawbacks, such as negatively influencing reaction time and impairing a service member's ability to work and function**.**

In contrast, continuous peripheral nerve blocks have no addiction potential, produce no side effects, and do not influence cognitive functioning whatsoever. Furthermore, continuous peripheral nerve blocks are now relatively ubiquitous within the United States, although applied nearly exclusively to provide acute post-injury/surgical analgesia.[37] Uncontrolled series suggest that treatment of phantom limb pain in the immediate post-amputation period with hospital-based CPNB may decrease the incidence of chronic phantom pain.[26,27] Functional magnetic resonance imaging has documented an association between phantom pain reduction with single-injection (limited duration) peripheral nerve blocks and reorganization of cortical pain mapping abnormalities.[21,23] Our own randomized, double-masked, placebo-controlled, crossover pilot study suggests great promise in dramatically reducing or completely resolving chronic, intractable phantom limb pain of both the upper and lower extremities with CPNB. Furthermore, this treatment may be safely provided on an ambulatory basis in the comfort of patients' own homes.[31]

If the proposed study demonstrates that ambulatory CPNB is an effective treatment for intractable phantom limb pain, the resulting impact in treating the consequences of traumatic amputation will be **immediate and profound, as healthcare providers within the United States Armed Forces and Veterans Affairs Medical Centers already have expertise placing and managing perineural catheters**.[5,6,25,62-64] While the healthcare providers of the U.S. Armed Forces are adept at placing perineural catheters and managing ambulatory CPNB, these are currently provided exclusively in the acute setting—to treat pain immediately following a battlefield injury or surgery—and not chronic, intractable phantom limb pain.[3,5,6,25,43,62-64] Because there is little technical difference in providing CPNB for acute versus chronic pain, **the thousands of U.S. Veterans and active duty personnel suffering from intractable phantom pain could be treated relatively easily, rapidly, and with negligible additional costs if ambulatory CPNB is demonstrated to be an effective treatment.** The proposed clinical trial directly and specifically addresses the FY12 DMRDP CTA-RPS Focus Area of Pain, in that ambulatory CPNB offers "the potential for significant impact on the alleviation of pain in wounded warriors;" and, is a novel application of an analgesic for "chronic pain resulting from combat-related injuries."

8. PROGRESS REPORT

Not applicable.

9. RESEARCH DESIGN AND METHODS

Study Design

This study is a multicenter, randomized, triple-masked (investigators, subjects, statisticians), placebo-controlled, parallel (with optional crossover), human-subjects clinical trial to determine if ambulatory CPNB is an effective treatment for intractable phantom limb pain following a traumatic limb amputation (Figure 1 below). There are a diverse group of recruitment sites that will provide a broad representative patients sample. Study participants will be recruited from five centers, including U.S. military, Veterans Affairs, and civilian university medical centers (one private, one public), within a wide geographic range including the Midwest and the East and West Coasts, providing a study sample with ethnic, racial, and socioeconomic diversity.

U.S. military medical centers:

- Walter Reed National Military Medical Center, Bethesda, Maryland
- Naval Medical Center San Diego, San Diego, California

Veterans Affairs medical center:

- Palo Alto Veterans Affairs Medical Center, Palo Alto, California

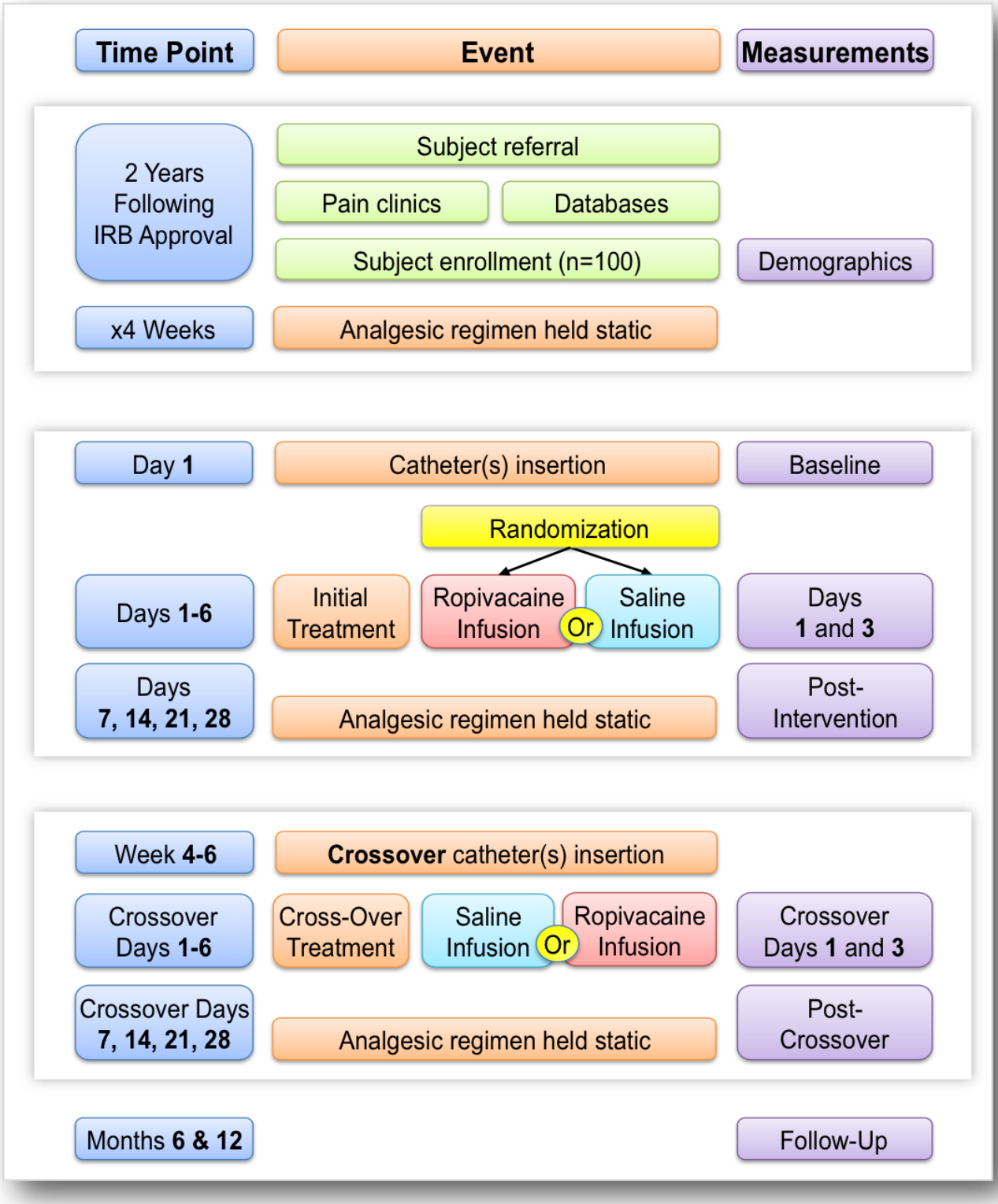
Civilian university medical centers:

- University of California San Diego, San Diego, California
- Cleveland Clinic, Cleveland, Ohio

The study will be prospectively registered on the clinicaltrials.gov website. The study will be overseen by both a medical monitor (Beverly Morris, RN, CNP, MBA; University of California San Diego, San Diego, California)—in essence a study subject advocate—as well as a Data Safety Monitoring Board (DSMB) comprised of the medical monitor, a physician familiar with the ethical conduct of clinical research (Peter Szmuk, MD; University of Texas Southwestern Medical School, Dallas, Texas), and statistician (Gerald Beck, PhD; Cleveland Clinic, Cleveland, Ohio). The medical monitor and DSMB will review enrollment, study data, protocol violations, adverse events, and oversee all aspects of the clinical trial every one and six months, respectively, through data analysis.

For inclusion/exclusion criteria please see Section 10 of this Research Plan.

Figure 1: Study Protocol



Enrolling centers will recruit patients from four sources: (1) surgical and chronic pain *databases; (2)* amputation, surgical, and chronic pain *clinic* referrals; (3) print and internet/web *advertisements*; and (4) *clinicaltrials.gov*. 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. In addition patients within multiple database types will be informed of the study *via* the postal service in the form of an IRB-approved letter. The letters will include research coordinator contact information for patients with interest in study participation.

Research coordinators will both explain the study protocol to interested patients, and subsequently review the inclusion/exclusion criteria. Subjects meeting inclusion/exclusion criteria and desiring study participation will be scheduled for catheter insertion at the nearest enrolling center. Written, informed consent will be obtained from each participant upon presentation for catheter insertion and before any measurements, data collection, and interventions. The method of documenting consent will be using written informed consent forms approved by the local IRB. Subjects will be asked to make no changes to their analgesic regimen for at least 4 weeks prior to the first catheter insertion, during the study infusion, and continuing until 4 weeks following their final catheter insertion: for the duration of the study, *all* patients will receive their pre-intervention analgesics. In other words, they will continue taking the same analgesics during the study period as they were receiving prior to the study period, including their standard rescue analgesics—the study protocol simply freezes the analgesic regimen for 8-12 weeks (depending upon elective participation in the crossover infusion).

Catheter insertion. Subjects will be asked to not eat or drink following midnight the night before catheter insertion. For women of childbearing age with the possibility of pregnancy, a sample of urine will be collected before any study interventions to confirm a non-pregnant state. Study participation will require that women of childbearing age with the possibility of pregnancy use a birth control method, such as abstinence, diaphragm, condom or intrauterine device to prevent pregnancy during the study. All subjects will have a peripheral intravenous catheter inserted, standard noninvasive monitors applied (blood pressure cuff, pulse oximeter, 5-lead ECG), and oxygen administered *via* a facemask. Intravenous and/or oral sedatives and analgesics such as midazolam and fentanyl will be titrated for patient comfort if necessary, while ensuring that patients remained responsive to verbal cues. The area(s) that will be subsequently covered by the catheter dressing will be removed of hair with a surgical clipper, if necessary. The catheter insertion site(s) will be cleansed with chlorhexidine gluconate and isopropyl alcohol, and a sterile, fenestrated drape applied. The amputation site dictates the anatomic location(s) and number of catheters: infraclavicular brachial plexus catheter (upper extremity amputation); sciatic/femoral catheters (below knee amputation).[31]

Upper extremity amputation. Subjects will be positioned in the supine position and receive an infraclavicular perineural catheter using a standard, previously published insertion technique.[67,68] With a low-frequency curved array ultrasound transducer in a sterile sleeve, the brachial plexus and axillary artery will be identified in a transverse cross-sectional (short axis) view. Once the optimal image of the brachial plexus cords is obtained, a local anesthetic skin wheal will be raised cephalad to the ultrasound transducer. A Tuohy-tip needle will be inserted through the skin wheal in-plane beneath the ultrasound transducer and directed caudad until the needle tip is between the axillary artery and the posterior brachial plexus cord. Normal saline (5-20 mL: the volume required is highly variable) will be injected *via* the needle to open the perineural space to allow subsequent insertion of a flexible 19 gauge perineural catheter 5 cm beyond the needle tip. The needle will be removed over the catheter, the catheter tunneled subcutaneously using a standard technique,[69,70] and the catheter affixed using a liquid adhesive, occlusive dressings, and an anchoring device.[31] Local anesthetic (30 mL, lidocaine 2% with epinephrine 2.5 μg/mL) will be injected *via* the catheter in divided doses with frequent aspiration.

Lower extremity amputation. Subjects will receive two perineural catheters: a femoral and popliteal-sciatic using standard, previously published insertion techniques.[71-73] The popliteal-sciatic catheter will be inserted first with the subject in the prone position, followed by the femoral catheter with the subject in the supine position. With a high-frequency linear array ultrasound transducer in a sterile sleeve, the target nerves will be

identified in a transverse cross-sectional (short axis) view: the sciatic nerve within the proximal popliteal fossa cephalad to the sciatic bifurcation, and the femoral nerve at the inguinal crease.[71-73] For each insertion, a local anesthetic skin wheal will be raised lateral to the transducer, and a Tuohy-tip needle will be inserted through the skin wheal in-plane beneath the ultrasound transducer and directed medially until the needle tip is posterior to each target nerve.[71-73] For each insertion, normal saline (5-20 mL: the volume required is highly variable) will be injected *via* the needle to open the perineural space allowing subsequent insertion of a flexible 19 gauge perineural catheter 5 cm beyond the needle tip. The needle will be removed over the catheter, and the catheter affixed as described previously for the infraclavicular catheter. Local anesthetic (20 mL, lidocaine 2% with epinephrine 2.5 μg/ml) will be injected *via* each catheter in divided doses with frequent aspiration.

The nerve block(s) will be evaluated 20 minutes following local anesthetic injection and the catheter insertion(s) considered successful when subjects have a decreased sensation to cold temperature (alcohol swabs) in the appropriate cutaneous distribution for each nerve. Subjects with successful catheter placement(s) will be retained in the study. With ultrasound-guidance, the authors have documented an initial catheter insertion success rate greater than 95%;[67,71,72,74-76] and any misplaced catheters are easily and accurately replaced.[37]

Treatment group assignment (randomization). Subjects will be allocated to treatment only after confirmation of a successfully-inserted perineural catheter(s), and will be randomized to one of two study solutions:

1. *ropivacaine 0.5%*
2. *normal saline (placebo)*

Randomization will be stratified by institution/hospital and amputation location (upper vs. lower limb) in a 1:1 ratio, and in randomly chosen block sizes. Randomization lists will be created using Statistical Analysis Software computer-generated tables by the University of California San Diego Investigational Drug Service. A randomization list for each enrolling center will be created by the University of California San Diego Investigational Drug Service, and uploaded to a secure, password-protected, encrypted central server. Investigational pharmacists at each institution will prepare all study solution as determined by these randomization lists, accessed by the pharmacists *via* the web-based, secure, password-protected, encrypted central server. Ropivacaine and normal saline are indistinguishable in appearance, and therefore investigators, subjects, and all clinical staff will be masked to treatment group assignment. Unmasking will not occur until statistical analysis is complete (termed "triple masking": subjects, investigators, and statisticians).

Study intervention. Electronic, programmable, portable infusion pumps will be used to administer perineural study solution at fixed rates for over 6 days.[36] Electronic, programmable, portable infusion pumps are currently used by the United States Armed Forces and have been used previously by the military to provide CPNB for up to 27 days immediately following limb trauma in soldiers returning from Iraq and Afghanistan.[25] Subjects will receive a total of 1,100 mL of study fluid from either one (upper extremity) or two (lower extremity) pump and external reservoir combinations. The continuous basal infusion rate will be determined by catheter location: femoral 2.5 mL/h; popliteal-sciatic 5 mL/h; and infraclavicular 7.5 mL/h (37.5 mg/h for both upper and lower extremity subjects). No patient-controlled bolus dose will be included.

Ambulatory infusion. Prior to discharge, subjects and their caretakers will be provided with verbal and written catheter/pump instructions, the telephone and pager numbers of an investigator available at all times, and a copy of the Institutional Review Board-approved consent form. Subjects with a lower extremity

amputation will be provided with crutches that they will be instructed to use until the day following catheter removal. Bathing will be permitted, as long as the catheter and infusion pump remain dry (e.g., sponge baths). Subjects will be discharged home with their portable infusion pump and perineural catheter *in situ*, and telephoned beginning the afternoon of catheter insertion and each subsequent day until catheter removal. During these calls, investigators will review gross sensory and motor function of the remaining limb; local anesthetic toxicity symptoms; infections signs and symptoms; catheter site appearance; infusion pump functioning (simply the volume infused displayed continuously and a flashing green light); and answer any questions.

With thorough catheter securing techniques such as catheter tunneling and others included in this protocol, the catheter dislodgement rate is less than 5% for infusions greater than one week, in both civilian[77] and military settings.[6] However, inadvertent premature catheter dislodgement does rarely occur.[37] In the proposed study, if premature dislodgement occurs, the subject may opt to have the catheter replaced as soon as can be arranged with the investigators. All subjects will be retained in their respective treatment groups for analysis per the intent to treat principle.

Six days following catheter insertion, the study fluid reservoir(s) will be exhausted and subjects or their caretakers will remove the perineural catheter(s) with instructions given by an investigator *via* telephone. This procedure encompasses simply removing the occlusive dressing and gently pulling on the exposed perineural catheter. Home removal has been used successfully for tens-of-thousands of previous patients,[31,37] and in one survey over 95% of patients responded that catheter removal was "easy" and that they would not have preferred to return for removal.[32] However, if a subject desires, the patient may return to the medical center for catheter removal by a health-care provider.

Optional crossover treatment. Four to sixteen weeks following the initial catheter insertion date, subjects ***may*** return for an optional repeated perineural catheter insertion ("crossover"), and receive 6 days of ambulatory infusion with the alternate solution (either ropivacaine 0.5% or normal saline), again in a double-masked fashion using the same protocol as described for the initial infusion. This option is provided irrespective of whether or not there is any perceived residual effect from the first infusion**. The crossover treatment is <u>not</u> required for study participation, as the primary analyses will include a parallel study design for the initial infusions.** 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; (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 ropivacaine 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 CPNB within four weeks of the initial infusion.

Following study completion, the results will be mailed to all enrolled subjects in written form using non-technical (e.g. "layperson") language.

Outcome measurements (endpoints). We have selected measurement instruments and 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.[78] ***The primary end point will be the difference in average daily phantom pain intensity at baseline and 4 weeks following the initial infusion*** *(measured with the Numeric Rating Scale as part of the Brief Pain Inventory).*[79] The primary analyses will compare the two treatments (inter-subject comparisons) during the initial perineural infusion in which half of the subjects will receive active drug (ropivacaine 0.5%), and the other half placebo (normal saline).

Endpoints will be evaluated at baseline and on the day following catheter insertion (Day 1; during infusion); as well as 7, 14, 21, 28 days following the initial catheter insertion (Table 1). These same time points will be evaluated following the second (crossover) catheter insertion begun 4-6 weeks after the initial catheter insertion. Subjects will also be evaluated 6 months and then 1 year after the initial infusion to evaluate longer-term treatment effects.

The questionnaire will differentiate among multiple dimensions of limb pain:

Residual limb ("stump") pain:	painful sensations localized to the portion of limb still physically present.[80,81]
Phantom limb sensations:	*non*-painful sensations referred to the lost body part.[80,81]
Phantom limb pain:	painful sensations referred to the lost body part.[80,81]

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 assess so-called "stump" pain as well. 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."[82] Exceptions will be on Day 1 for both the initial and crossover treatments that occur during the perineural infusions themselves, because at these time points the interest is in subjects' experiences with the infusion, and not prior to catheter insertion. During these two days, subjects will be instructed to respond for the previous 24 hours.

Table 1. Summary of post-enrollment assessments.

Subjects:	**All**						**Participating in Crossover ***						**All**	
Time Point Following:	**Initial** Catheter Insertion						**Crossover** Catheter Insertion						**Initial**	
Time Point (Days):	0	1	7	14	21	28	0	1	7	14	21	28		
Time Point (Months):													6	12
Brief Pain Inventory (for Phantom Limb Pain)	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Residual Limb Pain (NRS)	x	x				x	x					x	x	x
Patient Global Impression of Change Scale		x	x			x		x	x			x	x	x
Beck Depression Inventory	x					x	x					x	x	x
Frequency and Average Duration of:														
Non-Painful Phantom Sensations	x	x				x		x				x	x	x
Phantom Limb Pain	x	x				x		x				x	x	x
Residual Limb Pain	x	x				x		x				x	x	x
Masking Assessment						x						x		

* Second—or "crossover"—catheter insertion will occur between 4-6 weeks following the initial catheter insertion

Hypothesis 1: Phantom limb pain ***intensity*** will be significantly decreased 4 weeks following an ambulatory CPNB (as measured by the Numeric Rating Scale within the Brief Pain Inventory).

Pain intensity. 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.[79] 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, with 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[83] specifically—and following analgesic interventions.[84] In addition, NRS scores correlate well with other measures of pain intensity,[85] and demonstrate high test-retest reliability in chronic nociceptive and neuropathic pain states.[86] These NRS characteristics led to recent IMMPACT consensus recommendations for use of the 10-point NRS of pain intensity for chronic pain trials.[78]

Hypothesis 2a: Perception of **well-being** will be significantly improved 4 weeks following an ambulatory CPNB (as measured with the Patient Global Impression of Change Scale).

Health-related quality of life. While single-item measures of pain level/relief are currently the most reliable and valid options to measure pain intensity,[85,87] the multidimensional aspect of the pain experience has led consensus recommendations for use of "global" measures of improvement in chronic pain trials.[78] The Patient Global Impression of Change Scale is one such measure allowing patient evaluation of integrated treatment effects.[78] 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,[78] including studies specifically involving peripheral neuropathy.[78,88]

Hypothesis 2b: Physical and emotional **functioning** will be significantly improved 4 weeks following an ambulatory CPNB (as measured with 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."[85,87] This observation has led to consensus recommendations that "multiple core domains and related measures be considered in pain treatment trials,"[85] that "tap into a wider experience of pain over time and its impact on functioning and quality of life."[87] Therefore, the proposed trial will include the Brief Pain Inventory, an instrument that includes—in addition to pain intensity scales—seven measures evaluating pain's interference with physical and emotional functioning, such as sleep, relations with others, and enjoyment of life.[82,83] The Brief Pain Inventory has been used in countless clinical studies of chronic pain,[82] and validated specifically in neuropathic pain states.[83,89-91] This instrument is associated with minimal subject burden and is easily interpreted by patients of all ages and education levels.[83] It has high test-retest reliability and correlates well with much longer questionnaires, including the McGill measures and EuroQol.[83]

Hypothesis 2c: **Depression** will be significantly decreased 4 weeks following an ambulatory CPNB (as measured with the Beck Depression Inventory).

Multiple investigations demonstrate that factors such as anxiety and depression are strong predictors of pain intensity.[92,93] Therefore, the proposed study will evaluate additional psychosocial factors using the Beck Depression Inventory.[94] This 21-item instrument measures characteristic symptoms and signs of depression, requires only a 5th grade comprehension level to adequately understand the questions, demonstrating high internal consistency (0.73-0.92, mean of 0.86), reliability and validity.[95,96] Each of the 21 factors is rated on a 0-3 scale, and then summed to produce the total score of 0-63. Mild, moderate, and severe depression is defined with scores of 10-18, 19-29, and 30-63, respectively. While this instrument requires less than 10 minutes to complete, on average, it will be administered only at the initial baseline and four weeks following each perineural infusion (initial and crossover) to minimize subject burden and fatigue.

Additional pain-related data. Frequency and average duration of non-painful phantom sensations, phantom limb pain, and residual limb pain will be assessed.[83] In addition, supplemental analgesic use will be recorded, and other pain locations/severity will be evaluated using the NRS.[83] Lastly, to investigate masking adequacy, subjects will be queried four weeks following catheter insertion on the infusion type (active drug vs. placebo) they believe they received.

Data collection. Subject demographic and catheter insertion data will be uploaded from each enrolling center *via* the Internet to a secure,[97] password-protected, encrypted central server (Clinical and Translational Research Institute, University of California San Diego, San Diego, California).[98] The questionnaire for all subjects—regardless of enrolling center—will be administered by telephone from the University of California San Diego by research coordinators specifically trained in this instrument's application, minimizing inter-rater discordance. Staff masked to treatment group assignment will perform all assessments. This web-based data-collection protocol has been used successfully by the investigators for numerous previously published

multicenter clinical trials.[70,99-102]

Statistical Plan and Data Analysis

The randomized groups will be descriptively compared on baseline demographic and pain variables using descriptive statistics. In particular, groups will be considered well-balanced on a particular baseline variable if the standardized difference (difference in means or proportions divided by the pooled standard deviation) is less than $\sqrt{2/n}$, where n is the per-group sample size.[103] The primary analysis will be modified intention-to-treat, in which all randomized subjects who received any of the study treatment will be included and retained in their respective treatment groups.[104]

Hypothesis 1: Primary outcome. We will assess the average causal effect of ambulatory CPNB versus placebo on phantom limb pain intensity (average pain over past 72 hours) at 4 weeks after the initial perineural catheter insertion and subsequent infusion using analysis of covariance to adjust for baseline pain intensity and any imbalanced baseline variables (see above). Results will be summarized as the least squares difference in means at 4 weeks and 95% confidence interval. Mean and standard deviation change from baseline intensity will also be summarized. Similar analyses will be conducted for the secondary outcomes of current/present, worst and least phantom pain, as well as average and worst residual limb pain.

Secondary outcomes.
Hypothesis 2a. The randomized groups will be compared on the global measure of improvement (Patient Global Impression of Change Scale) at 4 weeks using the Mann-Whitney test. Proportional odds logistic regression will be used to adjust for any imbalanced baseline variables, as appropriate.
Hypothesis 2b. The randomized groups will also be compared at 4 weeks on the seven measures of Brief Pain Inventory which evaluate pain's interference with physical and emotional functioning. We will use a mixed effects multivariate model (random subject term, fixed treatment effect, unstructured correlation matrix) to first assess whether the treatment effect differs across the 7 measures (i.e., treatment-measure interaction). In presence of an interaction, each measure will be evaluated univariably. Otherwise, an overall treatment effect will be estimated from the mixed effects model as the primary result for this aim.
Hypothesis 2c. Analysis of covariance adjusting for baseline score will be used to assess the treatment effect of ambulatory CPNB versus placebo on depression at 4 weeks after randomization as measured by the Beck Depression Inventory.

Blinding assessment. We will assess the quality of the blinding of subjects to initial treatment assignment by comparing the randomized groups on the proportion guessing correctly at 4 weeks (after measuring primary outcome pain scores) as to which group they were originally assigned; a Pearson's chi-square test will be used.

For all analyses, alternative statistical methods will be used if the assumptions of the planned analyses are not met. For instance, t-tests or regression analyses on the change or percent change from baseline (depending on which is less correlated with baseline score) will be used instead of analysis of covariance when comparing groups on the 4-week outcomes if the treatment group-by-baseline interaction is significant. Transformations of the data or Mann-Whitney test or other non-parametric procedures will be used if the assumptions of normality and/or equal variances are not met.

Crossover phase. Beginning 4-6 weeks after the original randomization, requesting subjects will receive the opposite treatment from that received in their original randomization, and the same measurements will be collected through 28 days (see Table 1). This option will allow all subjects the opportunity to receive the study treatment. Although a completely unbiased assessment of the average causal effect will not be possible for this

phase because the second treatment will be voluntary, and crossover will thus likely be requested more often from those receiving placebo in the first phase, we will still descriptively report the average treatment effect from those choosing to cross over (but no testing will be done; unbiased average causal effect will be obtained from the first phase).

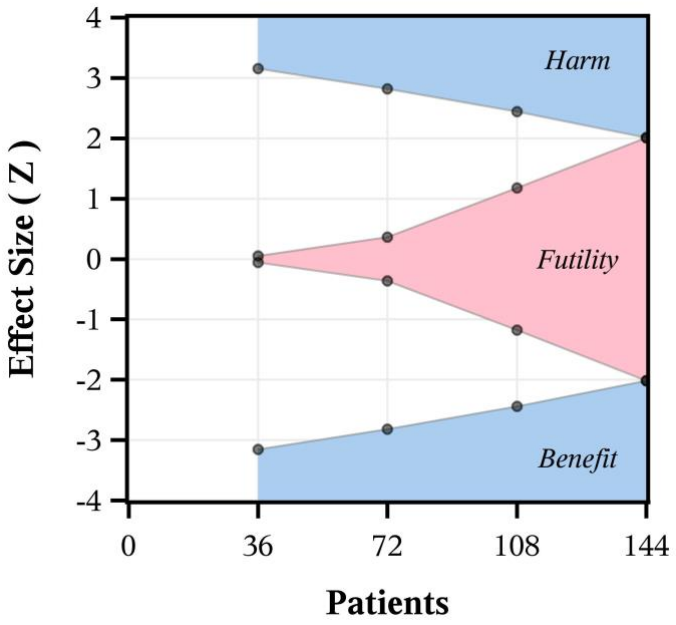
More importantly, we will estimate the variability in the individual causal effects of CPNB versus placebo using this crossover design. Variability of the individual causal effects cannot be directly estimated in a parallel group study (e.g., from the main portion (Aim 1) of this study we can only directly estimate the average causal effect), since only the outcome for the single treatment received is measurable for each subject. However, estimation of the variability of the individual causal effects from the crossover study, quantified as the standard deviation of within-subject differences on treatment versus placebo, will provide valuable information about the heterogeneity of the treatment effect across subjects associated with CPNB treatment of phantom limb pain. We will also use regression models to explore whether any baseline factors are associated with higher or lower causal effects of treatment.

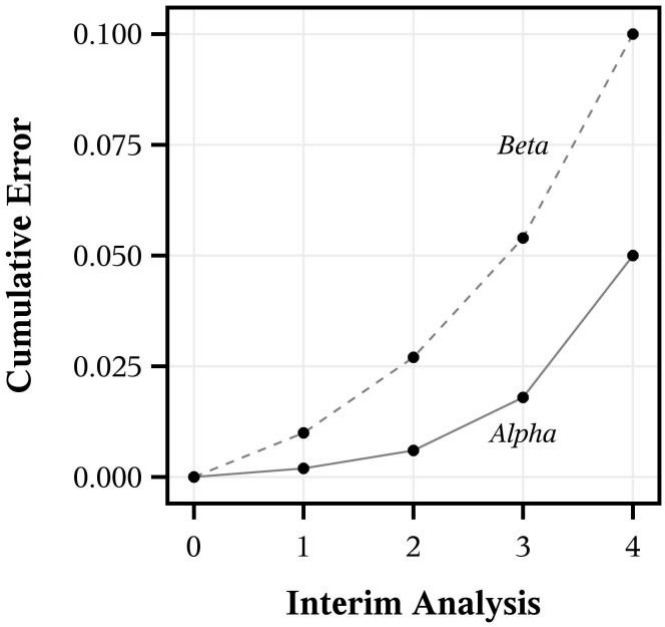
Long-term follow-up. Data for all outcomes will also be collected at 6 and 12 months post randomization. Due to the crossover design, we will not be able to directly assess the treatment effect of CPNB versus placebo on these outcomes. Rather, we will descriptively assess the change from the initial baseline to both 6 and 12 months for various groups of subjects: 1) all who received the study drug either initially or in the crossover, 2) initial control subjects who were not crossed over; 3) initial control subjects who were crossed over; 4) initial treated subjects who were not crossed over; 5) initial treated subjects who were crossed over.

Dropouts. At most about 7% of subjects in each group are expected to drop out of the study before reaching the 28-day primary outcome assessment (based on our unpublished pilot study of pre-emptive CPNB use for surgical amputation, for which we observed 1 of 15). Since the current study will consist of volunteers traveling to the centers for enrollment and catheter insertion, we expect even less. For those missing 28-day data we will use the last-observation-carried-forward method if the brief pain inventory was measured at either 14 or 21 days. Otherwise, we will use intent-to-treat and conservatively assign the best observed score to the placebo group and the worst score for the treated group subjects. We do not expect any appreciable effect of dropouts on either the power of the study or the unbiasedness of study results.

Interim analyses. We will conduct interim analyses to assess efficacy (rejecting null) and futility (rejecting alternative) at each 25% of the maximum enrollment using a group sequential procedure. Specifically, a gamma spending function will be used with parameters -4 and -2 for efficacy and futility, respectively.[105] Thus, boundaries at the 1st through 4th analyses for efficacy (futility in parentheses) will be $P \leq 0.0016$ ($P > 0.9572$), $P \leq 0.0048$ ($P > 0.7186$), $P \leq 0.0147$ ($P > 0.2389$) and $P \leq 0.0440$ ($P > 0.0440$), Figures 7 and 8.

Figure 7. Boundaries for efficacy and futility. **Figure 8. Alpha and beta spending functions**





Type I error. We will use a parallel gatekeeping procedure to control the study-wide type I error at 0.05.[106] For this procedure we therefore a priori prioritize the study outcomes into ordered sets, as Aim 1, Aim 2a, Aim 2b and then Aim 2c. Analysis will proceed in that order, and testing will proceed through each "gate" to the next set if and only if at least one outcome in the current set reaches significance. The significance level for each set will be 0.05 times a cumulative penalty for non-significant results in previous sets (i.e., a "rejection gain factor" equal to the cumulative product of the proportion of significant tests across the preceding sets). Within a set, a multiple comparison procedure (Bonferroni correction) will be used as appropriate to control the type I error at the appropriate level. SAS statistical software (Carey, North Carolina), R programming language (The R Project for Statistical Computing) and East 5.3 software (Cytel Inc.) will be used for all analyses.

Sample size considerations. Our sample size estimate is based on the primary specific aim of whether the addition of an ambulatory CPNB decreases phantom limb pain intensity resulting from a traumatic amputation compared with current standard-of-care treatment at 4 weeks following the ambulatory CPNB. Receiver operating characteristic curve analyses demonstrate that changes from baseline of at least 1.7 along a 10-point NRS accurately identified patients who rated improvements as "much improved" or more, compared with those who perceived no change or worsening following analgesic interventions.[88] Multiple additional studies confirm this degree of reduction as clinically meaningful to individual patients with chronic pain.[85,107,108]

Therefore, we power our study to be able to detect group differences in mean change from baseline of 1.7 points or more on the NRS. Based on a conservative standard deviation estimate for each group of 3.0 at 28 days, a correlation of 0.50 between baseline and follow-up NRS, a two-sided test at the 0.05 significance level, power of 0.90, and 4 equally spaced analyses (3 interim and 1 final, as needed), a maximum of 72 subjects in each group (N=144 total) is required (East 5.3 software, Cytel Inc). The expected sample size for this group sequential design (i.e., average sample size over thousands of such trials, stopping when a boundary is crossed) is a total of 100 under the alternative and 102 under the null hypotheses. Table 2 reports boundary crossing probabilities at each of the 4 analyses for this design, assuming that either the null or alternative hypotheses were true. For example, there is a cumulative 8%, 37% and 75% chance of crossing a boundary at the 1st, 2nd, and 3rd analyses, respectively, if the alternative hypothesis were true. However, if the true standard deviation at 28 days were smaller, say 2.5 instead of 3.0, then the cumulative probability of stopping for efficacy at the 1st, 2nd and 3rd analyses, respectively, would increase to 16%, 55% and 88% under the alternative hypothesis.

Table 2. P-value boundaries and boundary crossing probabilities for group sequential design.

Fraction of Maximum Accrual	Cumulative Accrual	Alpha Spent	Beta Spent	P-value Boundaries		Boundary Crossing Probabilities	
				H0	H1	Under H0	Under H1
0.250	36	0.002	0.010	0.0016	0.9572	0.044	0.083
0.500	72	0.006	0.027	0.0048	0.7186	0.269	0.290
0.750	108	0.018	0.054	0.0147	0.2389	0.485	0.379
1.000	144	0.050	0.100	0.0440	0.0440	0.202	0.248

10. HUMAN SUBJECTS

Inclusion criteria: Adults of at least 18 years of age, (1) with an upper or lower limb traumatic or surgical amputation at least 12 weeks prior to enrollment distal to the mid-humerus or hip (femoral head remaining), respectively, and including at least one metacarpal or metatarsal bone, respectively; (2) who experience at least moderate phantom limb pain—defined as a 2 or higher on the Numeric Rating Scale (NRS; 0-10, 0= no pain; 10=worst imaginable pain)—at least 3 times each week for the previous 8 weeks in a single limb (in the case of multiple amputations); (3) accepting of an ambulatory perineural infusion for 6 days; (4) willing to avoid changes to their analgesic regimen as well as elective surgical procedures from 4 weeks prior to and at least 4 weeks following the initial catheter placement (preferably 4 weeks following the optional second/crossover catheter insertion as well); and (5) have a "caretaker" who will transport the subject home following the catheter insertion(s), and remain with the subject for the first night of the infusion(s).

Exclusion criteria. (1) Known renal insufficiency (creatinine > 1.5 mg/dL); (2) allergy to the study medications; (3) pregnancy; (4) incarceration; (5) inability to communicate with the investigators; (6) morbid obesity (body mass index > 40 kg/m^2); (7) comorbidity that results in moderate-to-severe functional limitation (American Society of Anesthesiologists physical status classification > 2);[66] and (8) possessing any contraindication to ambulatory perineural catheter placement or perineural local anesthetic infusion, such as a current infection at the catheter insertion site, immune-compromised status of any etiology, uncontrolled anxiety/panic disorder, inability to contact the investigators during the perineural infusion (e.g., lack of telephone access). Of note, multiple amputations and phantom limb pain in more than one location are not exclusion criteria. Due to the increased explosive power of modern armaments, multiple-amputation casualties are now a frequent occurrence within the U.S. military. It is therefore vitally important to assess the effectiveness of ambulatory continuous peripheral nerve blocks on phantom pain for this patient population.

There are no restrictions on race, ethnicity, or sex; and, individuals of all races, ethnicity, socio-economic status, and sex are of interest and will be enrolled. We anticipate a very diverse subject pool that generally represents the demographics of the population of the United States given the wide-variety of recruitment sites: military, Veteran, and civilian; the East, Midwest and West coasts; private, State supported, and Federally supported; as well as academic and nonacademic. Adult subjects (18 years and older) will be enrolled. There will be no participants from vulnerable populations, such as pregnant women, children, or prisoners. The enrollment goal for this study is 144 subjects evaluable subjects with measured primary endpoints distributed over the five enrolling centers. Therefore, to allow for drop-outs and other unevaluable subjects, we anticipate enrolling a total of 180 subjects over the five enrolling centers, and 60 subjects specifically at UC San Diego.

11. RECRUITMENT

Potential study subjects will be introduced to the proposed investigation by one of their healthcare providers, receive a letter from the investigators (subjects within amputee databases), or view an advertisement in clinic, a support group, print publication, or website. They will contact either a research coordinator or site director for additional details on the study. This will include the study inclusion and exclusion criteria. Subjects will be asked to contact the study coordinator or site director again with further questions or to request enrollment (subjects can request enrollment during the first phone contact, but they will not be asked to enroll at that time to avoid any perceived "pressure" to enroll). If a subject desires enrollment, the study coordinator will schedule a catheter-insertion appointment at the enrolling center.

Of note, various hospitals are planning in the future on sending out information regarding this study to their own patients who previously underwent limb amputations. These hospitals will request IRB approval from their own IRBs to participate in this way. The reason that these hospitals will need to obtain their IRBs' approval is because they want to extract from their own databases the names and addresses of their previous patients who received an amputation at their own hospital; and, then send these individuals information regarding the multicenter study on phantom limb pain being overseen by UCSD. Potential subjects who are interested in participating will contact the UCSD P.I. (myself) or another IRB-approved UCSD investigator/coordinator for further information and screening. Any subjects who desire participation and fit all criteria will be enrolled at one of the four currently-IRB-approved enrolling institutions for this multicenter study.

So, these external hospitals' involvement will be to simply produce the mailing labels for their previous amputation patients, and affix these labels to pre-stamped envelopes containing IRB-approved (both UCSD and other IRBs) study information. Once mailing these envelopes, the external hospitals' IRBs will be closed, as they will have nothing further to do with the study. They are involved in no enrollment, treatment, data collection, or data analysis. They are simply querying their database for patients and then producing address labels (affixing these labels to envelopes and dropping them all in the U.S. mail).

These institutions include:

- MD Anderson (University of Texas)
- Rush University
- Northwestern University
- Hospital of Special Surgery (New York)
- Mayo Clinic (Rochester)
- University of Washington
- UC Los Angeles
- UC San Francisco
- Oregon Health and Sciences University
- University of Utah
- Columbia University
- Brigham and Women'sCancer Center
- Massachusetts General Hospital
- Johns Hopkins
- University of Texas Southwestern
- Brooke Army Medical Center
- Memorial Sloan Kettering Cancer Center

- Duke University
- Dartmouth University
- Thomas Jefferson University
- University of Florida

12. INFORMED CONSENT

If a patient desires study participation, written, informed consent will be obtained (either at that time in clinic if seen in person, or upon presentation for catheter placement but prior to all interventions and outcome measurements). An investigator or research coordinator specifically trained in both study details and appropriate consenting procedures will attain verbal and written informed subject consent. The method of documenting consent will be using written informed consent forms approved by the IRB.

13. ALTERNATIVES TO STUDY PARTICIPATION

Patients can decline enrollment. If they do so, they will still receive their current analgesics.

14. POTENTIAL RISKS

1. Infection. Since the catheter will be left in place for 6 days, there is a very small risk (<1%) of infection.
2. Falling. The risk of falling due to the perineural infusion in lower extremity amputees is currently unknown, since this intervention has not been prospectively investigated previously.
3. Catheter dislodgement. There is a risk of the catheter being accidentally and prematurely dislodged or becoming disconnected from the infusion pump.
4. Catheter retention (<0.01%)
5. Bleeding (<0.01%)
6. Nerve injury (<0.01%)
7. Local anesthetic toxicity (<0.01%)
8. Loss of confidentiality

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

Planned procedures for protecting against or minimizing potential risks include:

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

During the infusions, the subjects will be contacted through the day following catheter removal by an investigator or research coordinator, and subjects will have a physicians' pager and cellular phone numbers available to respond 24 hours/day and 7 days/week until the day following catheter removal. This procedure has proven effective for ambulatory surgical patients with perineural local anesthetic infusions. Patients will be called daily and asked about signs and symptoms of catheter infection. Should a catheter become infected, the catheter will be removed and oral antibiotics prescribed. Subjects with lower extremity infusions will be given crutches to use during the infusion itself.

If a catheter is accidentally and prematurely dislodged or disconnected from the infusion pump, the patient will turn off the infusion pump and may opt to have the catheter/pump replaced as soon as possible with the investigators.

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. The study is triple-masked and placebo-controlled, so in case of a complication related to the delivery of study fluid, the investigational pharmacy will be contacted to determine study group. However, in case of a severe adverse event or medical emergency, the pump can be disabled, the tubing clamped shut, and/or the catheter removed—so that infusion may be stopped without knowing study group assignment.

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

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Disposition of data. The original, hard-copy signed informed consent forms and case report forms will be stored within the local site director's locked office, where they will remain for at least 7 years. These hard copies will not be mailed or otherwise transferred. Data will be uploaded and stored in one location: the central servers of Department of Outcomes Research at the Cleveland Clinic, a department dedicated completely to clinical research. This department has a full-time Research Electronic Data Capture (REDCap) programmer dedicated to developing REDCap databases and providing support for clinical trials. REDCap is a relational database for data entry and auditing. This is a web-based application designed exclusively to support data capture for research studies. The Department of Outcomes Research at the Cleveland Clinic web servers are encrypted and password-protected with multiple firewalls to the standards of the National Institutes of Health. Of note, the servers are backed up every night. In the case of a disk failure, only data written to the files since the last backup will be subject to loss and can be easily restored. Databases are protected through electronic measures using a multi-layered, but simple approach: all study related files will reside on the database server rather than on individual hard disk drives and the files will be protected by the operating systems features against general access. User names will be password protected. The electronic data will remain within the Department of Outcomes Research for 7 years following study completion. The UCSD research coordinator may receive training at the UCSD CTRI in REDCap use. With such training, up to six hours of user support is provided without recharge. However, technical and most user support will be provided by the Cleveland Clinic. The USAMRMC (United States Army Medical Research and Materiel Command) is eligible to review study records at any time.

Each local site will transfer certain PHI to the UCSD research coordinator who will make all data collection phone calls for all subjects. PHI transferred will include the subject's name, phone numbers, and study ID. This information will be transferred via a secure online system known as the Army Missile and Research, Development and Engineering Command Safe Access File Exchange System (AMRDEC SAFE). AMRDEC SAFE is a secure, password-protected, system that the military has approved, and requires, for the transfer of such data. Civilian centers may use this system if access is granted, or fax to a locked office with access restricted only to the UCSD study coordinator and the PI.

Sharing study results. Following study completion, all subjects will be provided with the study results in written form and in language appropriate for non-medical individuals. In addition, the master dataset will be de-identified.

17. POTENTIAL BENEFITS

For subjects randomized to receive normal saline: There will be no difference between being in this study and "standard" care. Therefore, there is no potential for direct benefits during this infusion. However, all subjects will be offered the option of participating in the cross-over arm of the study, in which case they would receive

active treatment (see below).

For subjects randomized to receive ropivacaine: It is our hope that patients have a permanent decrease in their phantom limb and/or stump pain.

Possible benefits to others: Future patients may benefit if it is determined that ambulatory perineural local anesthetic infusion decreases phantom limb and/or stump pain. There are hundreds-of-thousands of individuals world-wide who suffer from these debilitating conditions, and finding an effective treatment would be a tremendous step forward in treating these individuals.

18. RISK/BENEFIT RATIO

Chronic phantom limb and stump pain cause significant disability for patients, and there is currently a dearth of reliable treatments for this debilitating pain. Since infection is the largest risk of this intervention, and there have no previous cases of permanent negative sequelae due infection reported in the literature, we believe the potential risks to be minimal compared to the potential benefits.

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

19. EXPENSE TO PARTICIPANT

None.

20. COMPENSATION FOR PARTICIPATION

Subjects will receive $100 following each catheter insertion plus $50/day during the 6-day infusion(s). Compensation following catheter insertion will be provided prior to home discharge; while infusion compensation will be mailed via the United States Postal Service following catheter removal. Currently, military regulation 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 civilian and Veterans.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Brian M. Ilfeld, MD, MS, is a board-certified anesthesiologist with fellowship training in and 12 post-training years experience with regional anesthesia and ambulatory perineural local anesthetic infusion. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC Medical Centers. Dr. Ilfeld, or another study investigator with similar training/experience in perineural techniques, will either place or supervise a resident/fellow placing perineural catheters. Dr. Ilfeld, or another clinical investigator, will follow all subjects during their perineural infusion. As Principal Investigator, Dr. Ilfeld will be responsible for preparing and submitting the required Institutional Review Board documents, overseeing the implementation of the protocol, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations. He will assure that all regulatory requirements are met and assure that all personnel receive appropriate training to properly complete the protocol. As Principal Investigator, he will be responsible for the overall management of this study across all sites, as well as for the well-being of

study subjects. Lastly, Dr. Ilfeld will be responsible for liaising with and reporting to the study DSMB; as well as authoring resulting manuscripts.

Beverly A. Morris, RN, CNP, MBA, is the head of nursing education for the entire University of California at San Diego hospital system, a Certified Nurse Practitioner and experienced multicenter clinical trial researcher. As the investigation's medical monitor, and Data Safety Monitoring Board Member, Ms. Morris will oversee volunteer recruitment, volunteer enrollment, data collection, data storage, data analysis, and will report any discrepancies or problems to the Institutional Review Boards of both the enrolling center and lead center (University of California San Diego), as well as the Army Human Research Protections Office. The Medical monitor will have the authority to stop the clinical trial at any time, and take any actions necessary to protect the safety and well-being of research volunteers until the Institutional Review Boards can assess the situation(s). In addition the Medical monitor will review all adverse events and provide a written opinion regarding the relationship and outcome of any unanticipated problems related to participation, serious adverse events, and subject deaths.

Gerald Beck, PhD, is a biostatistician with over 35 years of academic experience, and head of the Section of Clinical Trials Design and Analysis within the Department of Quantitative Health Sciences at the Cleveland Clinic. As a statistician, Dr. Beck will review data on an ongoing basis, including the interim analyses described within the statistical section of the protocol. As a member of the Data Safety Monitoring Board, Dr. Beck will help oversee volunteer recruitment, volunteer enrollment, data collection, data storage, data analysis, and will report any discrepancies or problems to the Institutional Review Boards of both the enrolling center and lead center (University of California San Diego), as well as the Army Human Research Protections Office.

Steven P. Cohen, MD, is a Colonel within the United States Army Reserves, a fellowship-trained chronic pain medicine practitioner, the Director of Chronic Pain Research at the Walter Reed Army National Military Medical Center, an Associate Professor of Anesthesiology at both civilian and military academic centers, and the Chief of Anesthesia Services, 48th Combat Support Hospital, Fort Meade. As such, Dr. Cohen is extraordinarily familiar with the issues of both post-amputation phantom limb pain in wounded Warriors and clinical research within United States military care centers. As a Co-Investigator and Steering Committee member, Dr. Cohen will help develop the study protocol, oversee study implementation and execution, review data and results for the interim and final analyses, and coauthor resulting manuscripts.

Daniel I. Sessler, MD, is the Chair of the Department of Outcomes Research at the Cleveland Clinic—a department dedicated completely to clinical research. Dr. Sessler founded and directs the Outcomes Research Consortium, anesthesia's largest and most productive clinical research organization. As a Co-Investigator and Steering Committee member, Dr. Sessler will help develop the study protocol, oversee study implementation and execution, review data and results for the interim and final analyses, and coauthor resulting manuscripts.

James C. Eisenach, MD, is a fellowship-trained specialist in chronic pain medicine, has over 30 years of experience performing clinical human subjects research, and is currently a Professor of the Wake Forest University Translational Science Institute, and Vice Chairman for Research of this institution. Dr. Eisenach is the current Editor-in-Chief of the journal Anesthesiology, the highest-impact medical journal of the field of Anesthesiology. As a Co-Investigator and Steering Committee member, Dr. Eisenach will help develop the study protocol, oversee study implementation and execution, review data and results for the interim and final analyses, and coauthor resulting manuscripts.

Edward J. Mascha, PhD is a biostatistician in the Departments of Anesthesiology, Outcomes Research, and Quantitative Health Sciences at the Cleveland Clinic. Dr. Mascha has over 20 years of experience in designing, conducting and analyzing clinical trials and collaborating on a wide variety of research projects. His work in

anesthesiology has included design and analysis of numerous single and multi-centered clinical trials in many areas of perioperative medicine. As a Co-Investigator and Steering Committee member, Dr. Mascha will help develop the study protocol, oversee study implementation and execution, review data and results for the interim and final analyses, and author resulting manuscripts. As the study biostatistician, he will oversee the statistical design, statistical programming, data integrity and analysis, and reporting of the data to the Principal Investigator, medical monitor, and DSMB. Lastly, Dr. Mascha will assist in the database design and coauthor resulting manuscripts.

Michael L. Kent, MD, an anesthesiologist in the Department of Anesthesiology at Walter Reed National Military Medical Center (WRNMMC), is fellowship-trained in regional anesthesia and acute pain medicine, including the insertion of perineural catheters and management of ambulatory CPNB. Dr. Kent has provided care to hundreds of wounded Warriors with traumatic amputations. He is an expert in the application of ambulatory CPNB and the care of gravely injured United States Armed Services members. Dr. Kent holds a license to practice medicine in Maryland. Dr. Kent has medical privileges at WRNMMC. As the site director for the WRNMMC, Dr. Kent will be responsible for hiring, training, and overseeing a research coordinator, preparing and submitting the required Institutional Review Board documents, implementing the protocol at WRNMMC, outreach to prospective subjects, communicating among referring clinics, enrolling subjects, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations. As the site director, he will assume responsibility for organization and management of the study at this site. He will assure that all regulatory requirements for this site are met and assure that all personnel receive appropriate training to properly complete the protocol. He will be responsible for all decisions regarding the conduct of the protocol in consultation with the project Principal Investigator, as necessary; and coauthor resulting manuscripts.

Sarah J. Madison, MD, is an anesthesiologist and Director of Education for residents and fellows in the Division of Regional Anesthesia in the Department of Anesthesiology at the University of California at San Diego. Dr. Madison is fellowship trained, specializing in regional anesthesia. Dr. Madison holds a license to practice medicine in California. Dr. Madison has medical privileges at the UC Medical Centers. As the site director for UCSD, Dr. Madison will be responsible for outreach to prospective subjects, communicating among referring clinics, enrolling subjects, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations. She will be responsible for all decisions regarding the conduct of the protocol in consultation with the project Principal Investigator, as necessary; and coauthor resulting manuscripts.

Amanda Monahan, MD, is an anesthesiologist in the Division of Regional Anesthesia in the Department of Anesthesiology at the University of California at San Diego. Dr. Monahan is fellowship trained, specializing in regional anesthesia. Dr. Monahan holds a license to practice medicine in California. Dr. Monahan has medical privileges at the UC Medical Centers. Dr. Monahan will be responsible for outreach to prospective subjects, communicating among referring clinics, enrolling subjects, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations. She will be responsible for all decisions regarding the conduct of the protocol in consultation with the project Principal Investigator, as necessary; and coauthor resulting manuscripts.

Bahareh Khatibi, MD, is an anesthesiologist in the Division of Regional Anesthesia in the Department of Anesthesiology at the University of California at San Diego. Dr. Khatibi is fellowship trained, specializing in regional anesthesia. Dr. Khatibi holds a license to practice medicine in California. Dr. Khatibi has medical privileges at the UC Medical Centers. Dr. Khatibi will be responsible for outreach to prospective subjects, communicating among referring clinics, enrolling subjects, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations.

She will be responsible for all decisions regarding the conduct of the protocol in consultation with the project Principal Investigator, as necessary; and coauthor resulting manuscripts.

Edward R. Mariano, MD is the Chair of the Division of Anesthesiology at the Palo Alto VA, and also holds an academic position of Associate Professor at Stanford University. Dr. Mariano is fellowship trained in regional anesthesia and acute pain medicine and a recognized expert of ultrasound-guided perineural catheter insertion and the management of ambulatory CPNB. Dr. Mariano has extensive experience running multicenter clinical trials. Dr. Mariano holds a license to practice medicine in California. Dr. Mariano has medical privileges at the Palo Alto VA. As the site director for the Palo Alto VA, Dr. Mariano will be responsible for hiring, training, and overseeing a research coordinator, preparing and submitting the required Institutional Review Board documents, implementing the protocol at the Palo Alto VA, outreach to prospective subjects, communicating among referring clinics, enrolling subjects, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations. As the site director, he will assume responsibility for organization and management of the study at this site. He will assure that all regulatory requirements for this site are met and assure that all personnel receive appropriate training to properly complete the protocol. He will be responsible for all decisions regarding the conduct of the protocol in consultation with the project Principal Investigator, as necessary; and coauthor resulting manuscripts.

Alparslan Turan, MD is an anesthesiologist in the Departments of Outcomes Research and Anesthesiology at the Cleveland Clinic. Dr. Turan is fellowship trained in chronic pain medicine, and is extraordinarily experienced in regional anesthesia, including the insertion of perineural catheters and management of ambulatory CPNB. As a member of the Outcomes Research Consortium, Dr. Turan has extensive experience with multicenter clinical trials. Dr. Turan has cared for hundreds of patients with post-amputation phantom limb pain. Dr. Turan holds a license to practice medicine in Ohio. Dr. Turan has medical privileges at the Cleveland Clinic. As the site director for the Cleveland Clinic, Dr. Turan will be responsible for hiring, training, and overseeing a research coordinator, preparing and submitting the required Institutional Review Board documents, implementing the protocol at the Cleveland Clinic, outreach to prospective subjects, communicating among referring clinics and database managers, enrolling subjects, inserting perineural catheters, managing the subsequent perineural infusions, subject oversight, as well as reporting adverse events and protocol violations. As the site director, he will assume responsibility for organization and management of the study at this site. He will assure that all regulatory requirements for this site are met and assure that all personnel receive appropriate training to properly complete the protocol. He will be responsible for all decisions regarding the conduct of the protocol in consultation with the project Principal Investigator, as necessary; and coauthor resulting manuscripts.

Jennifer Padwal, MS is a medical student at UCSD who will be assisting with outreach to prospective subjects, communicating among referring clinics, enrolling subjects, collecting data, entering data into electronic databases, as well as reporting adverse events and protocol violations. She will be working under the direct supervision of Dr. Brian Ilfeld, the Principal Investigator.

Baharin Abdullah is a research coordinator with the UCSD CTRI and she will be working on this project in that capacity.

Cindy Wen, BS, is a research coordinator with the UCSD Department of Ophthamology and she will be working on this project in that capacity.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

Dr. Ilfeld is supported by a Department of Defense grant award (W81XWH-13-2-009) which helps to support his nonclinical time and the product used in this investigation. Start date for this grant was December 26, 2012 and termination date will be December 25, 2016. Please contact Christina Richardson, grants specialist, at 619-543-5291 for information regarding this DOD grant. All funding for this investigation is provided by the DOD.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable.

26. IMPACT ON STAFF

Participants will be enrolled by research coordinators specifically hired and trained for the study. Subjects receiving catheters at UCSD may be seen either at the CTRI, in which the unit is compensated via recharge mechanisms to monitor study subjects, or at Hillcrest Hospital. The services of a nurse will not be required, and therefore there will be no impact on clinical staff.

27. CONFLICT OF INTEREST

The Department of Defense is funding this study in its entirety. There is no financial or otherwise conflict of interest for any of the investigators.

28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES
Not applicable.
29. OTHER APPROVALS/REGULATED MATERIALS
Not applicable.
30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT
Not applicable; surrogate consent will not be accepted.

Version date: May 11, 2011