Official Title: Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Department of Defense Funded Pragmatic Clinical Trial

NCT: 04713098

Document date: November 12, 2020

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, which was unchanged and only one version exists; (with a summary of changes between what was originally planned vs. actual analysis).

Original Protocol

Dated October 2020, prior to enrollment of the first participant

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

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

Version date: 9/30/2013

1. PROJECT TITLE

Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain

2. PRINCIPAL INVESTIGATOR

Brian M. Ilfeld, MD, MS

3. FACILITIES

UCSD hospitals and the UCSD CTRI

4. ESTIMATED DURATION OF THE STUDY

Six years (1 year regulatory and preparation, 3.5 years enrollment, 1 year follow-up, 0.5 year analysis and publication)

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

Postoperative pain is usually treated with opioids that have undesirable and sometimes dangerous side effects (e.g., vomiting and respiratory depression)—and yet over 80% of patients still experience inadequate pain relief. A novel, non-pharmacologic analgesic technique—percutaneous peripheral nerve stimulation (PNS)— holds extraordinary potential to greatly reduce or obviate opioid requirements and concurrently improve analgesia following painful surgery. This technique involves inserting an insulated electric lead adjacent to a target nerve through a needle prior to surgery using ultrasound guidance. Following surgery, a tiny electric current is delivered to the nerve resulting in potent pain control without any cognitive or adverse systemic side effects whatsoever. The electrical pulse generator (stimulator) is so small it is simply affixed to the patient's skin. The leads are already cleared by the US Food and Drug Administration to treat acute (postoperative) pain for up to 60 days; and, since percutaneous PNS may be provided on an outpatient basis, the technique holds the promise of providing potent analgesia outlasting the pain of surgery—in other words, the possibility of a painless, opioid-free recovery following surgery. We propose a multicenter, randomized, quadruple-masked, placebo-controlled, parallel-arm clinical trial to determine the effect of percutaneous PNS on postoperative analgesia and opioid requirements, as well as physical and emotional functioning, the development of chronic pain, and ongoing quality of life. This investigation has a strong potential to dramatically reduce or obviate postoperative opioid requirements and their resultant negative effects on both individuals and society; while concurrently improving analgesia, increasing the ability to function in daily life, decreasing the risk of transition from acute to chronic pain, and improving quality of life.

6. SPECIFIC AIMS

UG3 Planning Phase

The initial UG3 feasibility study will be a randomized, double-masked, placebo-controlled, parallel-arm, human subjects pilot study with two Specific Aims:

Specific Aim 1 (UG3): To determine the **feasibility** and **optimize** the protocol of the Implementation Phase (UH3) multicenter clinical trial that will compare percutaneous PNS with usual and customary opioid-based analgesia following moderate-to-severely painful ambulatory surgery.

Specific Aim 2 (UG3): To ***estimate*** the **treatment effect** of percutaneous PNS on pain and opioid consumption following moderate-to-severely painful ambulatory surgery compared with usual and customary opioid-based analgesia. This will allow determination of the required **sample size** of the definitive multicenter clinical trial of the Implementation Phase (UH3).

UH3 Implementation Phase

The primary Specific Aim of the trial is to determine the effect of percutaneous PNS on postoperative **opioid** requirements and **analgesia** following moderate-to-severely-painful ambulatory surgery (under the usual conditions in which PNS will be applied, making this a "pragmatic trial"). Secondary Specific Aims are to determine the effect of percutaneous PNS on physical and emotional **functioning**, **chronic pain**, and **quality of life** following moderate-to-severely-painful ambulatory surgery.

Hypothesis 1 (UH3)*:* **Opioid** consumption will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia (measured in oral morphine equivalents).

Hypothesis 2 (UH3): Surgical **pain** will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Hypothesis 3 (UH3)*:* Physical and emotional **dysfunction** due to pain will be decreased in the 12 months following ambulatory surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the Brief Pain Inventory).

Hypothesis 4 (UH3)*:* The incidence and intensity of **chronic pain** will be decreased 4 and 12 months following surgery with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Hypothesis 5 (UH3)*:* **Quality of life** will be improved 1,4 and 12 months following surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the World Health Organization Quality of Life-BREF Instrument).

7. BACKGROUND AND SIGNIFICANCE

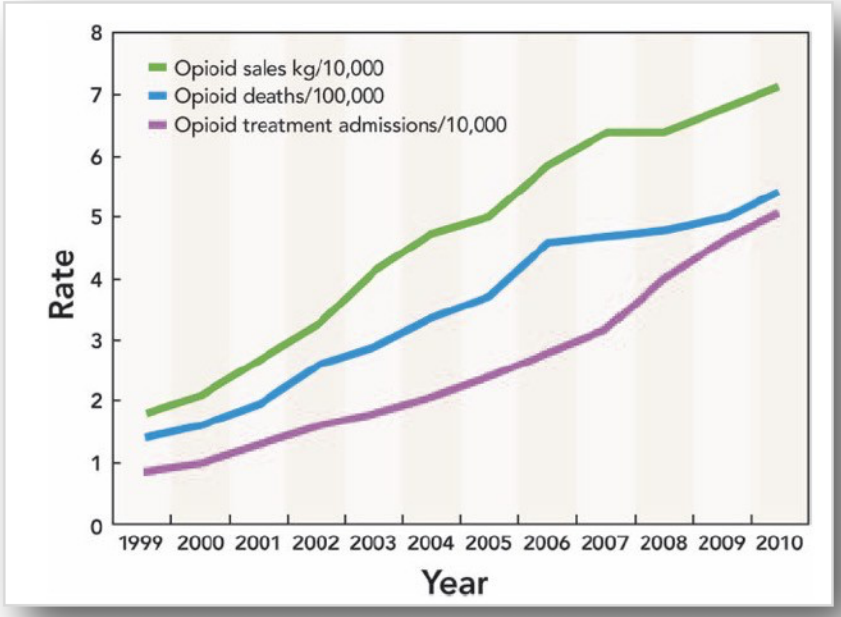
Background. There are tens-of-millions of ambulatory surgical procedures performed in the United States annually. Over 80% of patients experience inadequate pain relief following surgery with

consequences for both individuals and society. For patients, inadequate postoperative analgesia results not only in suffering, but also an increased risk of comorbidity (e.g., perioperative myocardial infarction), inferior rehabilitation, and the transition from acute pain to persistent ("chronic") post-surgical pain [incidence: 10-50%]. Persistent post-surgical pain frequently results in decreased productivity and a strain on personal relationships, as well as an increased risk of depression, chronic low-back and joint pain, obesity, and accelerated onset of cardiovascular disease. For society as a whole, inadequately-treated acute pain is a burden to the healthcare system, requiring increased healthcare provider time and the costs of readmission for ambulatory patients. Furthermore, persistent post-surgical pain not only increases medical care costs, but decreases overall economic output: the economic toll for chronic nonmalignant pain is over $100-billion annually within the United States.

Clearly, inadequately-controlled post-surgical pain is a substantial problem, which is intimately related to a reliance on perioperative opioids use—the foundation of postoperative analgesia for over a century. Unfortunately, opioids have significant undesirable consequences for both individuals and society. Frequent systemic side effects such as nausea, vomiting, and pruritus are irritants; but some effects may be fatal, such as cognitive impairment[13] and respiratory depression (with life-threatening hypoventilation requiring naloxone administration occurring in 1 of 333 patients). And, even minor ambulatory surgical procedures can lead to chronic opioid use, with significant negative consequences such as hyperalgesia, dependence and decreased quality of life.

The toll of opioids on society cannot be overemphasized. In the last 20 years the rate of prescription opioid diversion, abuse, addiction, and overdose has multiplied dramatically (**Figure 1**), with the overall economic cost of opioid abuse within the United States in excess of $70-billion annually. Over 5-million people within the United States use prescription analgesics without medical need or prescription, and this rate has more than doubled in the last 20 years. In excess of 28,000 deaths due to overdose occurred within the United States in 2010, a 700% increase in less than 2 decades. Shockingly, 65-80% of current heroin-dependent users began their addiction by abusing prescription opioids.

Figure 1. Rates of opioid analgesic sales, unintentional overdose deaths, and addiction treatment admissions.[1]



Considering ***4-20% of all opioid pills prescribed within the United States are diverted and abused—almost 500-million doses annually***—the supply of oral opioids is of great concern. Nearly 80% of abused oral opioids were originally intended for someone else, with most obtained from a friend or relative. Unused prescription opioids are so ubiquitous that "young recreational

users do not have to venture outside their immediate social networks to find those who will sell or share pills." Indeed, it has been conclusively demonstrated that both the abuse of opioids and extent of diversion are relative to their prescriptive availability.

Wounded service members and Veterans have been disproportionately affected, given that addiction is especially common in populations with co-existing psychopathology (e.g., depression, post-traumatic stress disorder). 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. Within the U.S. Armed Services, the most-commonly abused class of prescription drugs is opioids, ***with the incidence of prescription drug misuse increasing from 2% to 11% between 2002 and 2008.*** 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 to what most now describe as an epidemic. The Department of Defense has prioritized non-addictive analgesic modalities for pain states that are currently treated primarily with opioids. Thus, inadequately-controlled postoperative pain and opioid diversion/abuse are significant challenges for Armed Services members, Veterans and their families. A new treatment for postoperative pain is desperately needed to both improve analgesia and concurrently decrease dependence on opioids.

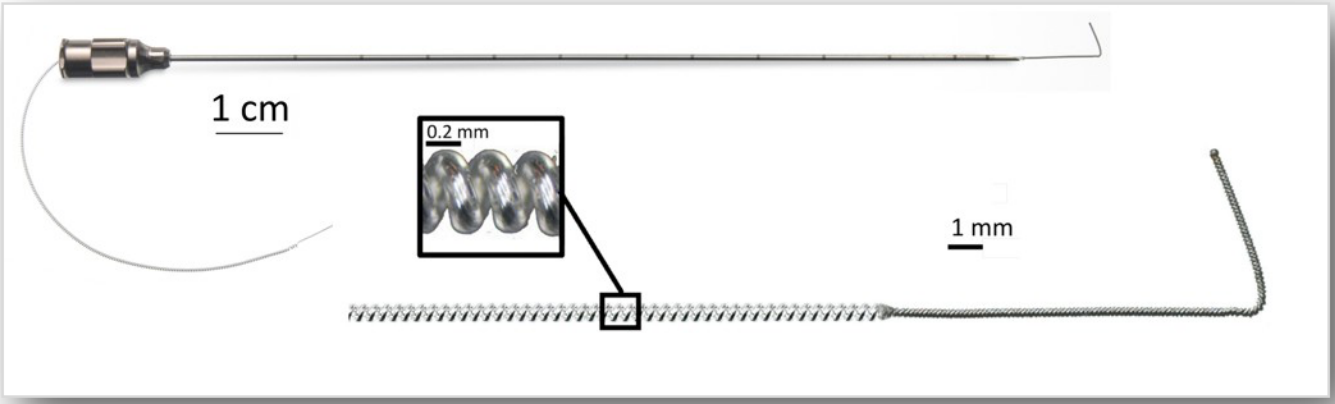
One analgesic alternative—**percutaneous peripheral nerve stimulation (PNS)**—holds extraordinary promise to improve post-surgical analgesia while concurrently decreasing or obviating opioid requirements; and, all without any adverse systemic side effects.

Many hypotheses have been proposed to explain the analgesic effects of stimulation—also termed "***neuromodulation***", but Melzack and Wall's "gate control theory" is the most common and accepted theory: electric current stimulates large-diameter afferent peripheral nerves that subsequently interrupt communication (the "gate") from small-diameter pain fibers to the central nervous system at the level of the spinal cord. Neuromodulation has a long history—and demonstrated efficacy—in the management of ***chronic*** pain using surgically implanted spinal cord and peripheral nerve stimulators.

However, the application of neurostimulation to ***postoperative*** pain states has been limited by the invasive nature of the available electrical leads: conventional units typically require multiple electrodes in close proximity to the peripheral nerve that require invasive and time consuming surgery to place and subsequently remove. Stimulation with electrodes placed on the skin (transcutaneous electrical nerve stimulation, "TENS") has been investigated previously to determine if it has the potential to avoid these limitations. However, activation of pain fibers in the skin greatly limit the degree of tolerated current that can be delivered by TENS and creates an undesirable analgesic 'ceiling'.

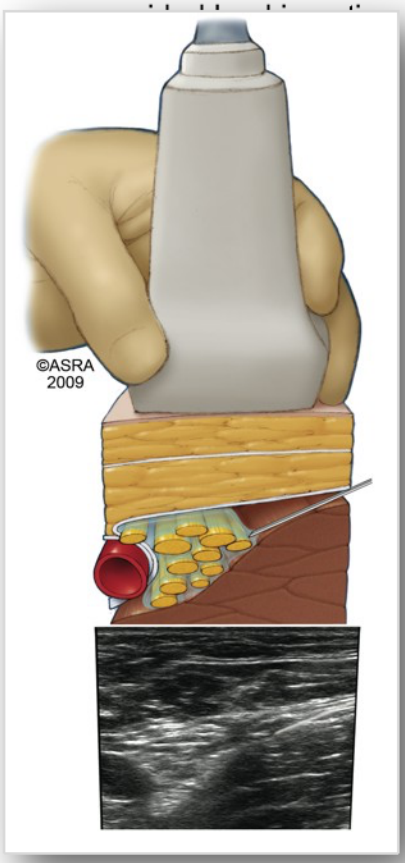
To apply neurostimulation to treatment postoperative pain, optimally this modality should be administered without an open surgical incision. ***Extremely small, insulated electrical leads have now been developed that permit relatively rapid percutaneous insertion through a needle***, obviating the need for a surgical incision (**Figure 2**, following page; MicroLead, SPR Therapeutics, Cleveland, OH).[1]

Figure 2. A 12 cm, 20 g needle with a pre-loaded helically-coiled insulated electrical lead (inset: a magnified lead).



Using ultrasound to guide placement, a lead may be reliably inserted 0.5-3.0 cm from a peripheral nerve using similar landmarks and accepted approaches as for peripheral nerve block or perineural catheter administration (**Figure 3**).

Figure 3. Ultrasound-



An external stimulator—so small that it may be directly adhered to the skin (**Figure 4**)—subsequently delivers a small electric current through the insulated lead to the target nerve.

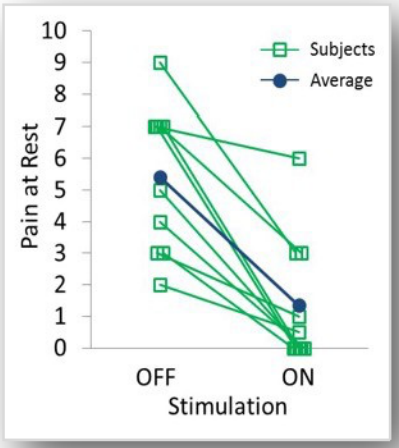
Figure 4. A stimulator (inset) and setup for percutaneous peripheral nerve stimulation



Preliminary studies and pilot data. We recently published 2 series of cases describing the first uses of percutaneous PNS to treat postoperative pain [funded, in part, by NIH 1R44AG052196].[1,2] We used the novel leads described previously that were recently cleared by the US Food and Drug Administration (FDA) to treat acute pain within the peripheral nervous system. A total of 10

individuals were included who experienced pain difficult to control with oral analgesics between 6 and 97 days following total knee arthroplasty. Using ultrasound guidance, a femoral and/or sciatic nerve electrical lead was inserted, depending on where the majority of pain originated (anterior vs. posterior knee, respectively). Pain scores were recorded before and after the stimulator was activated. ***Of these 10 subjects, 5 had complete resolution of their pain, 4 experienced a 57-67% decrease, and 1 a 14% reduction (Figure 5).***[1,2]

Figure 5. Pilot data



The significant analgesia demonstrated in these 10 subjects led our group to investigate the possibility of using PNS immediately following surgery. Seven patients had femoral and sciatic nerve leads inserted using ultrasound guidance prior to undergoing total knee arthroplasty.[3] A single-injection adductor canal nerve block was administered using a long-acting local anesthetic, and surgical anesthesia provided with a spinal or general. The following morning stimulators were reconnected to the leads and current delivered continuously for up to 6 weeks. Patients were discharged home with their leads *in situ*. In 6 of 7 subjects (86%), the average of daily pain scores across the first 2 weeks was well controlled and mild (<4 on the 0-10 Numeric Rating Scale for pain). Of the 5 subjects with data on opioid use, ***the median time to complete opioid cessation was only 8 days, with 100% of subjects opioid-free 1 month following surgery.*** This is a dramatic improvement compared with the typical median time to cessation of nearly 2 months (vs. 8 days), with a 1-month opioid-independence rate of 11-33% (vs. 100%) for patients having the same surgical procedure within the United States.

The opioid-sparing potential of PNS for painful ambulatory surgery is illustrated by one subject who, following a hallux valgus repair ("bunionectomy")—one of the most painful orthopedic procedures performed—reported only mild pain and **required no opioids** from the recovery room through her entire period of convalescence with two weeks of sciatic nerve stimulation (unpublished data). Due to the ability to provide PNS in ambulatory patients and a treatment duration of up to 30 days, the PNS system outlasted the pain of surgery. These remarkable results led our team to submit an application to the Department of Defense (FY16 Peer Reviewed Orthopaedic Research Program) to support a clinical trial investigating the use of percutaneous PNS to improve function and rehabilitation following orthopedic **trauma** of the lower extremity using knee arthroplasty as a model.

Significance. In contrast to that submission and our previous work involving inpatient knee arthroplasty, the present application proposes applying percutaneous PNS to the most painful ***ambulatory*** surgical procedures to improve postoperative analgesia and dramatically reduce opioid requirements. If successful, benefits of ***decreasing pain in the immediate postoperative period*** may lead to a plethora of patient benefits beyond simply decreasing suffering and opioid requirements, including decreasing pain-related interference in activities of daily living and greatly improving physical rehabilitation—in and of itself critical in maximizing long-term outcomes. In addition, persistent post-surgical pain is correlated with increased perioperative pain; and, therefore, maximizing postoperative analgesia may decrease the incidence of transition from acute to chronic pain [incidence: 10-50%], reduce pain-related interference in activities of daily living, and improve quality of life.

Moreover, greatly reducing opioid requirements will not only reduce irritating systemic side effects such as nausea, vomiting, and pruritus; but diminish the incidence and severity of cognitive impairment and respiratory depression (with its associated mortality). Crucially, if opioid requirements can be dramatically reduced—or even eliminated—for the most painful ambulatory surgery, then opioid prescriptions may be drastically reduced or even eliminated for all related surgical procedures associated with a lower degree of pain. It is imperative that novel, non-opioid postoperative analgesic modalities are developed and disseminated considering:

- Tens-of-millions of ambulatory procedures are performed annually
- The number of surgical procedures is expected to grow exponentially in the coming decades
- Up to 20% of prescribed opioids—almost 500-million doses annually—are diverted and abused
- The abuse of opioids and extent of diversion are relative to their prescriptive availability
- Illicit opioid use has grown to epidemic proportions
- U.S. military personnel, Veterans and their families are disproportionately affected by these catastrophic trends with the incidence of prescription drug misuse increasing from 2% to 11% in the six years leading to 2008, and this trend continues unabated.

Ultrasound-guided percutaneous PNS has been used to treat chronic pain (e.g., phantom limb pain),[4] has demonstrated extraordinary potential to provide potent postoperative analgesia and concurrently reduce opioid requirements in our pilot studies, and is already cleared by the US FDA for use in treating post-surgical pain. Most importantly—and in contrast to opioids—***it has no abuse/addiction potential, produces no adverse systemic side effects, and does not influence cognitive functioning whatsoever.***[4] Consequently, we propose an initial pilot study phase (UG3) followed by a definitive randomized, quadruple-masked, placebo-controlled, parallel design, human subjects pragmatic clinical trial to determine the effect(s) of ultrasound-guided, percutaneous PNS on postoperative **pain, opioid requirements,** and **functioning/quality of life** following painful ambulatory surgical procedures.

8. PROGRESS REPORT

The pilot study (UG3) results: Cumulative opioid consumption for the first 7 postoperative days for the stimulation group (n=31) was a median [IQR] of 5 [0,30] versus 48 [25,90] mg for the sham group (n=34), ratio of means 0.20 (0.08, 0.50); P<0.001). Patient average pain score over the first 7 days for the stimulation group was a mean (SD) of 1.1 (1.4) vs. 3.1 (2.3) for the sham group, difference in means (95% CI) of -1.7 (-2.4, -1), P<0.001).

9. RESEARCH DESIGN AND METHODS

We propose a ***feasibility study*** during the initial 2-year Planning Phase [UG3] and multicenter, randomized, quadruple-masked (investigators, subjects, statisticians, manuscript authors), placebo-controlled, parallel arm, human-subjects ***pragmatic clinical trial*** period during the subsequent 4-year Implementation Phase [UH3] to determine if ultrasound-guided percutaneous peripheral nerve stimulation (PNS) greatly reduces or obviates postoperative opioid requirements while concurrently decreasing surgical pain. For the entire duration of the funding period we will comply with policies and practices developed by the Work Groups of the NIH-DoD-VA Pain Management Collaboratory, and we will work with the Coordinating Center in providing relevant information and material. We have included a diverse group of recruitment sites that will provide a broad, representative patient sample of active duty military members and their families. Study participants will be recruited from 6

centers, including both U.S. military and civilian medical centers within a wide geographic range, providing a study sample with ethnic, racial, and socioeconomic diversity.

U.S. military medical centers:

- Brooke Army Medical Center [San Antonio, Texas]
- Fort Bragg [Fayetteville, North Carolina]
- Naval Medical Center San Diego [San Diego, California]
- Walter Reed National Military Medical Center [Bethesda, Maryland]

Civilian university medical centers:

- University California San Diego [San Diego, California]
- Cedars Sinai [Los Angeles, California]

The study protocol and materials will be approved by each center's Institutional Review Board; and, the investigation will be prospectively registered on the clinicaltrial.gov website. The study will be overseen by a Data Safety Monitoring Board comprised of two physicians familiar with the ethical conduct of clinical research and one biostatistician. The DSMB will review enrollment, study data, protocol violations, adverse events, and oversee all aspects of the clinical trial.

UG3 Planning Phase

The initial UG3 feasibility study will be a randomized, double-masked, placebo-controlled, parallel-arm, human subjects pilot study with two Specific Aims:

Specific Aim 1 (UG3): To determine the **feasibility** and **optimize** the protocol of the Implementation Phase (UH3) multicenter clinical trial that will compare percutaneous PNS with usual and customary opioid-based analgesia following moderate-to-severely painful ambulatory surgery.

Specific Aim 2 (UG3): To ***estimate*** the **treatment effect** of percutaneous PNS on pain and opioid consumption following moderate-to-severely painful ambulatory surgery compared with usual and customary opioid-based analgesia. This will allow determination of the required **sample size** of the definitive multicenter clinical trial of the Implementation Phase (UH3).

Therefore, the protocol for the UG3 Planning Phase feasibility study and the UH3 Implementation Phase pragmatic trial will be identical, with the exception of any improvements determined by the UG3 study.

Enrollment. Surgeons at each enrolling center will identify potential study subjects at preoperative patient visits. Surgeons will be seeing patients as part of regular medical care, and therefore this protocol will adhere to Health Insurance Portability and Accountability Act (HIPAA) regulations. Patients meeting inclusion and exclusion criteria will be presented with the study, and prospective study subjects desiring additional information will be required to give permission for a research coordinator to contact them to adhere to HIPAA requirements. Research coordinators will review the study protocol in detail with interested prospective subjects; and, for subjects desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or

interventions. The method of documenting consent will be using written informed consent forms approved by the local Institutional Review Board.

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 [this is standard for the surgery regardless of study participation]. 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 until lead removal. Anthropomorphic and demographic characteristics as well as baseline end points will be recorded/measured.

Table 1. Anatomic locations for electrical leads and peripheral nerve blocks.

Surgical Location	Surgical Procedures	Lead Location	Peripheral Nerve Block Location
Shoulder	• Rotator cuff repair	Brachial plexus roots/trunks	Brachial plexus roots/trunks
Foot or ankle	• Hallux valgus correction • Ankle arthrodesis or arthroplasty	Sciatic	Popliteal sciatic [saphenous nerve block optional]

Lead insertion. Intravenous fentanyl (0-100 µg) and/or midazolam (0-2 mg) may be administered for patient comfort. Insulated leads will be inserted prior to peripheral nerve block administration. The lead insertion sites will be cleansed with chlorhexidine gluconate and isopropyl alcohol, and a sterile, fenestrated drape applied. A portable ultrasound paired with either a linear or curved array transducer within a sterile sleeve will be used for lead insertion (**Figure 9**). The target nerve will be imaged in a transverse cross-sectional (short axis) view and a local anesthetic skin wheal raised lateral to the ultrasound transducer.

Figure 9. Ultrasound-guided sciatic nerve lead insertion



Using an in-plane ultrasound guidance, we will implant approximately 1-2 cm from the target nerve a pre-loaded, monopolar, helically coiled, insulated lead (SPR Therapeutics, Cleveland, OH) attached to an external pulse generator (SPR Therapeutics) with a surface return electrode. Accurate lead placement will be confirmed with subject reports of comfortable sensations over the surgical site without eliciting muscle contractions.

Frequency will be set to 100 Hz, which is known to generate comfortable sensations and reduce pain compared to lower frequencies (2-50 Hz). Stimulus amplitude and pulse duration will be increased until the subject reports that comfortable sensations cover the surgical site (region in which pain is anticipated following surgery). Stimulation parameters will be adjusted to improve stimulation coverage and comfort. The lead will be affixed to the skin with a sterile occlusive dressing (**Figures 4 and 10**). The stimulator will be set to deliver a range of currents which subjects can control themselves. The stimulator will be removed until after surgery.

Figure 10. Inserted electrical lead secured under gauze and a dressing



Subjects will continue to receive usual and customary local anesthetic-based analgesia. Because percutaneous PNS does not induce a sensory block and therefore does not provide anesthesia for the surgical procedure itself, we will continue to provide subjects with preoperative single-injection local anesthetic-based peripheral nerve block(s) (**Table 1**; 20 mL of either ropivacaine 0.5% or bupivacaine 0.5% with epinephrine 1:400,000). In addition, surgeons will be permitted to infiltrate the surgical area with local anesthetic (bupivacaine HCl).

Treatment group assignment (randomization). Subjects will be allocated to a treatment only after confirmation of successfully inserted electrical leads; and will be randomized to one of two possible treatment groups (**Figure 11**):

(1) **Current** delivered via the electrical lead(s) [Experimental group]
(2) **No current** delivered via the electrical lead(s) [Control group]

Figure 11. Treatment groups.

Postoperative Day	0 [day of surgery]	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Experimental	Electric current														
Control	No electric current														

Randomization will be stratified by institution and anatomic lead location (**Table 4**) in a 1:1 ratio and in randomly chosen block sizes. Randomization lists for each enrolling center will be created by the Cleveland Clinic. Treatment group assignment will be conveyed to the enrolling sites via the same secure web-based system (RedCap) used to collect and collate all post-intervention endpoints (see "Data Collection" paragraph below). Stimulators are capable of programming to either (1) pass electrical current; or, (2) not pass electrical current. Importantly, these 2 modes (active and sham) are indistinguishable in appearance, and therefore investigators, subjects, and all clinical staff will be masked to treatment group assignment, with the only exception being the unmasked individual who programs the stimulator (and will not have subsequent contact with the subject). The unmasked personnel will have access to the randomization list on RedCap, program the stimulator appropriately (sham vs. active), and provide the individual subsequently interacting with the study subject with the device without indicating the treatment group.

Subjects will be informed that during postoperative active treatment with electrical current patients do not always have the sensations experienced during preoperative lead placement and once proper placement is confirmed with comfortable sensations, therapeutic levels of stimulation may be delivered sub-threshold (below the intensity required for sensation and still provide relief, which is factual/accurate). ***This protocol will ensure a randomized, double/quadruple-masked, sham/placebo-controlled trial.*** For the feasibility study (UG3), unmasking will occur 2 weeks following surgery to allow for protocol revisions, as necessary ("double masked" during data collection). In contrast, for the definitive pragmatic clinical trial (UH3) unmasking will not occur until statistical analysis and manuscript preparation are complete (termed "quadruple masked").

Intraoperative course. The primary surgical anesthetic will be a general anesthetic, spinal anesthetic or exclusively the preoperative single-injection peripheral nerve block(s). Anesthetics that are also analgesics such as ketamine will not be used: the only permitted analgesic will be intravenous fentanyl, which is anticipated to be minimal since all subjects will receive a single-injection peripheral nerve block immediately prior to surgery.

Postoperative course. Within the recovery room following surgery, the stimulators will be attached to the leads and activated. Operating and recovery room pharmacologic analgesic requirements will be recorded.

Post-hospital course. Prior to discharge, subjects and their caretakers will be provided with verbal and written instructions, the DVPRS scale (pain scale 0-10), and the telephone and pager numbers of a local investigator available at all times during the first two weeks of treatment. Subjects will be discharged home with their leads *in situ*. Subjects will be also be discharged with a prescription for immediate-release oral opioid, preferably oxycodone 5 mg tablets, taken for breakthrough pain. *Therefore, <u>all</u> patients of this study—regardless of the treatment arm they are randomized to—will continue to receive current usual and customary analgesia.* We will attempt to contact subjects the evening of POD 0 to review stimulator instructions, although it is not always possible due to logistical reasons such as a late recovery room discharge. Subjects will be contacted by telephone for end point collection beginning on POD 1. Lead removal will occur on postoperative day 14 (+/- 3 days) by healthcare providers. Similar to perineural catheters,[135] this procedure encompasses simply removing the occlusive dressing and gently pulling on the lead. For resistance during lead withdrawal, lidocaine 1-2% (1-10 mL) may be infiltrated around the lead to relax the peri-lead muscle. Following study completion, the results will be mailed electronically or by the United States Postal Service to all enrolled subjects in written form using non-technical language.

Outcome measurements (end points). We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain-related clinical trials by the World Health Organization and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.[136] ***Importantly, nearly all outcome measures are common data elements from the National Institute of Neurological Disorders and Stroke (NINDS).***[137] End points (**Table 2**) will be evaluated at baseline (at lead insertion prior to surgery), during the treatment period (postoperative days 1-11); and the follow-up period (postoperative day 18 and months 1, 4, and 12).

Table 2. Summary of post-enrollment assessments (color added for clarity)

Time Point:	Postoperative **Days**	Postoperative **Months**

	0	1	2	3	4	7	11	18	1	4	12
Opioid consumption previous 24 h	•	•	•	•	•	•	•	•	•	•	•
Average Pain [NRS]	•	•	•	•	•	•	•	•	•	•	•
Worst Pain [NRS]	•	•	•	•	•	•	•	•	•	•	•
Brief Pain Inventory, Short Form	•			•		•		•	•	•	•
Defense and Veterans Pain Rating Scale	•	•	•	•	•	•	•	•	•	•	•
World Health Organization **Quality of Life** Instrument	•								•	•	•
Post-Traumatic Stress Disorder Checklist (C)	•										
Masking Assessment		•									

Demographic and medical history. Subjects will have demographic and anthropomorphic data collected based on NINDS case report form General Core and Demographics Modules and Guidelines, including age, sex, height, weight, educational level, employment status, marital status, and U.S. military service (e.g., none, discharged, active). In addition, the medical history based on the common data elements of the NINDS Medical, Family, Behavioral History, History of Disease/Injury Event, and Prior and Concomitant Medications Sub-Domains will be collected, and include the mechanism of original injury, medications (including analgesics), previous surgical procedures, comorbidities, existing sensory deficits of the target nerve distribution, and preoperative pain levels measured on a Numeric Rating Scale for pain (including daily least, average, worst and current). In addition, since post-traumatic stress disorder (PTSD) may be associated with the severity of pain,[138] at baseline we will apply the PTSD Checklist (PCL-C), a 20-item self-report measure reflecting symptoms of PTSD validated in military,[139] Veteran,[140-142] and civilian populations.[143]

Postoperatively, surgical endpoints will be recorded such as surgical duration, tourniquet duration (if applicable), analgesic administration, anesthetic administered, and any sedative agents provided. In addition, subjects will have baseline end points measured including a pain score at the surgical site using the Numeric Rating Scale (NRS, 0-10). ***The remaining end points of Table 2 are described in detail under each Hypothesis in the UH3 Implementation Phase section description below.***

Data collection. Much of the surgical data from the day of surgery will be extracted from electronic health records to leverage data collection that occurs in health care delivery rather than requiring independent research data collection. Subject demographic, surgical and percutaneous PNS administration data will be uploaded from each enrolling center *via* the Internet to a secure,[144] password-protected, encrypted central server (RedCap, Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio).[145] All data collection following the day of enrollment (postoperative day 0)—regardless of enrolling center—will be collected by telephone from the University of California San Diego. Staff masked to treatment group assignment will perform all assessments.

UG3 Milestones. The 2-year UG3 feasibility period has explicit milestones (**Table 3**, following page) that are feasible, quantifiable, and scientifically justified to allow an assessment of progress. ***Each of the items listed in Table 3 and the following outline is considered a milestone and must be completed in order to proceed to the 4-year UH3 definitive, pragmatic clinical trial.***

Study Preparation. Finalize protocol with the Steering Committee, Site Directors, Significant Contributors, and NIH-DoD-VA Pain Management Collaboratory. Finalize common and individual site case report forms (each enrolling site will require forms that conform to its own specific requirements). In concert with the Principal Investigator, the Department of Outcomes Research (Cleveland Clinic, Cleveland, OH) will create the data-entry platform (database) used to store all study-related information. Equipment (e.g., electrical leads and stimulators) will be ordered for each enrolling center. Research Coordinators will be hired and trained at all enrolling centers. The Primary Investigator will visit each of the enrolling centers to train both Site Directors and Research Coordinators in all aspects of the study. In addition, a trained representative from the developer and manufacturer of the percutaneous PNS system (SPR Therapeutics) will travel to each enrolling center to train Site Directors and Research Coordinators on how to insert and manage the leads and stimulators. This will be done at the company's expense, and conform to all HIPAA requirements. Training will continue with successive subjects until both the representative and study personnel feel comfortable with the site's future enrollment without further training.

Table 3. Two-year **UG3** Planning Phase feasibility study **Timeline** (color added for clarity)

Funding Year:	**1**			**2**	
Months (within year):	**1-4**	**5-8**	**9-12**	**1-6**	**6-12**
Identify staff who will participate in NIH-DoD-VA Pain Management Collaboratory Work Groups	•				
Work with NIH-DoD-VA Pain Management Collaboratory to comply with approved policies and practices	•	•	•	•	•
Initiate DSMB and develop DSMB charter	•				
Report to medical monitor (monthly) and DSMB quarterly	•	•	•	•	•
Initiate and complete CRADAs at military treatment facilities	•	•	•		
Finalize preparation for UG3 feasibility study (details below)	•				
Hire/train research coordinators	•				
Prepare training/implementation documents and videos	•				
Prepare data-entry platform at the Cleveland Clinic	•	•			
Enrollment site IRB submissions, reviews and revisions	•	•	•		
NIH-DoD-VA oversight body submission	•	•	•		
Site visits and training by Principal Investigator			•		
Educate clinic contacts (e.g., surgeons) for referrals			•		
Order and prepare equipment			•	•	
Lead/stimulator training for all Site Directors by SPR Therapeutics			•	•	
Register study and update on clinicaltrials.gov				•	•
Subject enrollment (following IRB approval)				•	

Data collection, University California San Diego (Day 1 to Month 4)				•	•
Quality assurance				•	•
Address any ethical, human subject safety and oversight issues				•	•
Assess adequacy of protocol, data-entry platform, and study sites				•	•
Replace any study sites, if necessary					•
Data cleaning and statistical analysis					•
Revise pragmatic clinical trial (UH3) statistical section, as necessary					•
Revise protocol for pragmatic clinical trial (UH3), as necessary					•
If necessary, revise budget for pragmatic clinical trial					•
IRB revisions at enrolling centers and oversight agencies, if needed					•
Manuscript preparation: protocol description					•
Upload results to ClinicalTrials.gov					•
Final UG3 report to funding and oversight agencies					•

CRADA: Cooperative Research and Development Agreement

Regulatory Review and Approval Process. Of note, the entire first year of the funding period is currently designated for this purpose due to the often-prolonged period of time required for regulatory review and approval. However, enrollment may commence sooner if the regulatory process requires less than 1 year. This is probable since the stimulation system used in the proposed investigation is already cleared for use in treating acute pain, and therefore US FDA investigational device exemption approval is not needed and the proposed use in this study is on label. The final protocol will be formatted and then submitted to all enrolling site IRBs and the funding agency's oversight committee (e.g., U.S. Army Medical Research and Materiel Command Human Research Protection Office). The DSMB will be initiated which will design the DSMB charter describing role, reporting procedures, and meeting protocol. A Medical Monitor (DSMB Chair, "subject advocate") and DSMB members will receive quarterly reports prepared by the Principal Investigator (reviews project accomplishments, issues, problems, upcoming goals, adverse events, protocol deviations, etc.). The DSMB will review progress and recommends modification, continuation, or termination:

- Approval of the trial protocol before enrollment
- Review data in order to determine efficacy, futility, and safety, and to determine continuation
- Review data quality and data integrity
- Evaluate risk versus benefit by thorough examination of the data accumulated
- Determine whether the trial is proceeding as planned, the protocol is being followed, the recruitment of patients is on schedule, and data are being collected with the proper accuracy
- Review patient dropouts, if any, and make appropriate recommendations
- Determine whether safety concerns have been raised by the experimental or control treatments
- Modifications of the study protocol based upon the review of the safety data
- Suspension or early termination of the study or of one or more study arms because of serious concerns about patients' safety, inadequate performance, or rate of enrollment

- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines
- Optional approaches for executive committee and investigators to consider when the DSMB determines that the incidence of the primary study outcomes is substantially less than expected, such as recommendations to increase the number of trial centers or extend the recruitment period
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious

Study Implementation. The study will be registered on clinicaltrials.gov prior to enrollment of the first subject, and be kept updated. Research Coordinators will re-educate clinical contacts on ethical referral process and initiate the referral period. For the initial subject at each enrolling center, a trained representative from the developer and manufacturer of the percutaneous PNS system (SPR Therapeutics) will travel to each enrolling center to train both Site Directors and Research Coordinators in how to insert and manage leads and stimulators. For quality assurance, the Principal Investigator will review with the study team the entire first subject's course, from referral to enrollment to lead insertion to medical follow-up and adverse event or protocol deviation reporting.

Enrollment. The Research Coordinator or Site Director at each enrolling center will schedule lead insertions for that specific site. Baseline and day-of-surgery (postoperative day 0) data collection will occur at each enrolling site, with the case report forms faxed to the Principal Investigator at the University California San Diego using a secure fax machine in a locked office to protect personal health information. All data collection following the day of surgery will occur by telephone from the University of California San Diego, which will then enter all data to the database. For the UG3 feasibility study, the final data collection point for each subject will be at 4 months following surgery (the 12-month time point will be used for the definitive UH3 pragmatic clinical trial). Quality assurance will be ongoing by the University of California San Diego, which will monitor data for sources of error and report to the Medical Monitor (DSMB Chair) with written monthly reports. Each enrolling center will be expected to enroll at least 1 subject for each of the 3 possible lead locations (e.g., brachial plexus trunks) in each of the first two quarters of the 2nd year of the funding period. Combined, the 7 centers will enroll a total of 64 subjects as part of the feasibility study.

Preparation for the UH3 Clinical Trial. If one or more centers fails to enroll their designated subjects—for whatever reason(s)—other centers will make up this enrollment with coordination by the Principal Investigator. The 64-subject feasibility study will enable evaluation of the study intervention, protocol, case report forms, outcome measures, data-entry platform, Research Coordinators, Site Directors, and study oversight. Any changes deemed necessary by the Principal Investigator in concert with the DSMB, funding agency, Steering Committee, Site Directors and NIH-DoD-VA Pain Management Collaboratory Coordinating Center will be made to any aspect of the study design (such as the outcome measures or informed consent forms), including replacing any enrolling center that fails to demonstrate the ability to adequately enroll and execute the protocol (following completion of the UG3 phase, the Palo Alto VA and Cleveland Clinic were removed due to a complete lack of enrollment; and Cedars Sinai was added and successfully demonstrated the ability to enroll subjects). The data from the first 64 subjects will be cleaned by University of California San Diego and a statistical analysis performed by the study statistician (Edward Mascha, PhD) at the Department of Outcomes Research (Cleveland Clinic).

In concert with the NIH-DoD-VA Pain Management Collaboratory Coordinating Center, the statistical section for the subsequent UH3 pragmatic clinical trial will be revised to reflect the ***estimated treatment effect*** and treatment group means. For the initial submission, we have estimated the probable maximum sample size for budgeting and planning purposes; but, the results of the initial feasibility study will most-likely decrease the definitive UH3 pragmatic trial required sample size. The statistical section and budget will be revised to reflect any changes. Any revisions to the protocol or informed consent forms will be submitted to the DSMB, individual center IRBs and HRPO. A manuscript with the results of the pilot study will be prepared and submitted with the results concurrently uploaded to ClinicalTrials.gov. Lastly, a final UG3 period report will be prepared for the funding and oversight agencies.

UG3 Planning Phase Specific Aims. The investigation described above will accomplish the two Specific Aims of the UG3 Planning Phase:

Specific Aim 1 (UG3): To determine the **feasibility** and **optimize** the protocol of the Implementation Phase (UH3) multicenter clinical trial that will compare percutaneous PNS with usual and customary opioid-based analgesia following moderate-to-severely painful ambulatory surgery.

Specific Aim 2 (UG3): To ***estimate*** the **treatment effect** of percutaneous PNS on pain and opioid consumption following moderate-to-severely painful ambulatory surgery compared with usual and customary opioid-based analgesia. This will allow determination of the required **sample size** of the definitive multicenter clinical trial of the Implementation Phase (UH3).

UH3 Implementation Phase

The 4-year UH3 Implementation Phase will include a multicenter, randomized, quadruple-masked, placebo-controlled, parallel-arm, human subjects pragmatic clinical trial. The primary Specific Aim of the trial is to determine the effect of percutaneous PNS on postoperative **opioid** requirements and **analgesia** following moderate-to-severely-painful ambulatory surgery (under the usual conditions in which PNS will be applied, making this a “pragmatic trial”). Secondary Specific Aims are to determine the effect of percutaneous PNS on physical and emotional **functioning**, **chronic pain**, and **quality of life** following moderate-to-severely-painful ambulatory surgery. The definitive UH3 pragmatic clinic trial will use the same protocol as the UG3 Planning Phase feasibility study described above, with the addition of any revisions determined necessary following that initial investigation. We will work closely with the NIH-DoD-VA Pain Management Collaboratory Coordinating Center at all phases of the definitive pragmatic clinical trial, from preparation through data analysis and manuscript preparation.

The primary end points will be cumulative opioid consumption and average surgical pain (measured with a Numeric Rating Scale) within the first 7 postoperative days following recovery room discharge. The primary analyses will compare the two treatment groups, one of which will receive active stimulation while the other will receive no stimulation.

Hypothesis 1 (UH3): **Opioid** consumption will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia.

Opioid analgesic consumption will be recorded at all time points (**Table 2**), ***with one co-primary end point being the cumulative opioid dose in oral morphine equivalents for postoperative days 0-7*** (see statistical section for further details).

Hypothesis 2 (UH3): Surgical **pain** will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Current/present, worst, least, and average pain at the surgical site will be assessed using a Numeric Rating Scale (NRS) as part of the Brief Pain Inventory (short form). The Brief Pain Inventory is an approved NINDS common data elements Scale. The use of single items (e.g., average pain) in addition to the composite score is supported by the IMMPACT recommendations for assessing pain in clinical trials. The NRS will be recorded at all time points (**Table 2**), ***with one co-primary end point being the values of the "average" pain scores for the first postoperative week following recovery room discharge, collected on postoperative days 1, 2, 3, 4, and 7*** (see statistical section for further details). The NRS is a highly-sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain. The NRS has been demonstrated to be a valid and reliable measure following analgesic interventions. In addition, NRS scores correlate well with other measures of pain intensity, and demonstrate high test-retest reliability. These NRS characteristics led to recent IMMPACT consensus recommendations for use of the 10-point NRS of pain intensity for pain trials.

An additional instrument, the Defense and Veterans Pain Rating Scale (DVPRS), will be utilized. The DVPRS was developed specifically for—and subsequently validated in—active duty military and Veteran patient populations. Unfortunately, this new instrument has not been validated for repeated measures, and therefore will not be used as a primary end point for the current investigation. However, future pain-related investigations involving military personnel and Veterans will undoubtedly use the DVPRS, and we want the results of the current study to be comparable. Therefore, we will use the DVPRS as a secondary end point.

Primary end point: *In order to claim that percutaneous PNS is superior to usual and customary analgesia, at least one of Hypotheses 1 and 2 above must be superior while the other either superior or at least noninferior.*

Hypothesis 3 (UH3): Physical and emotional **dysfunction** due to pain will be decreased in the 12 months following ambulatory surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the Brief Pain Inventory).

The Brief Pain Inventory (short form) is an instrument specifically designed to assess pain and its impact on physical and emotional functioning. It has established reliability and validity, with minimal inter-rater discordance, is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement, and is an approved NINDS common data elements Scale. The Brief Pain Inventory is comprised of three domains: (1) *pain,* with four questions involving "worst", "average", "least", and "current" pain levels using a 0-10 NRS; (2) percentage of *relief* provided by pain treatments with one question [reported score is the percentage divided by 10 and then subtracted from 10: 0 = complete relief, 10 = no relief]; and, (3) *interference* with 7 questions involving physical and emotional functioning using a 0-10 Likert scale [0 = no interference; 10 = complete interference]: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The 4 questions addressing specific pain levels may be combined into a pain subscale (0-40); and, the 7 interference questions may be combined to produce an interference subscale (0-70), the latter of which will be of primary interest for this study. The use of single items (e.g., average pain), subscales, and the composite score (0 = optimal; 120 = worst possible) is supported by the IMMPACT recommendations for assessing pain in clinical trials. The Brief Pain Inventory has been used in countless clinical studies of chronic pain. This instrument is associated with minimal subject burden and is easily interpreted by patients of all ages and education levels.[160] It has high test-retest reliability and correlates well with much longer questionnaires, including the McGill measures and EuroQol.

***Hypothesis 4 (UH3)**:* The incidence and intensity of **chronic pain** will be decreased 4 and 12 months following surgery with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Current/present, worst, least, and average pain at the surgical site will be assessed using a Numeric Rating Scale (NRS) as part of the Brief Pain Inventory (short form).[151] The use of single items (e.g., average pain) in addition to the composite score is supported by the IMMPACT recommendations for assessing pain in clinical trials and is an approved NINDS common data elements Sub-Scale. Patient "worst" pain will be of primary interest at 4 and 12 months. As described previously, the NRS is a highly-sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain. The NRS has been demonstrated to be a valid and reliable measure following analgesic interventions.

***Hypothesis 5 (UH3)**:* **Quality of life** will be improved 1, 4, and 12 months following surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the World Health Organization Quality of Life-BREF Instrument).

While the primary goal of postoperative analgesics is in providing pain control, the most important outcomes for post-surgical patients are measures of well-being. These measures reflect the dimensions of health as they are conceptualized and valued by patients themselves. While health-related quality of life is a subjective concept, various instruments are available that convert health

status into quantifiable values. The World Health Organization Quality of Life (WHOQoL) Instrument is specifically designed to evaluate clinically important, patient-relevant changes in health-related quality of life. The WHOQoL-BREF was developed by the World Health Organization to focus on those aspects of life most important to patients and is composed of 24 questions assessing 4 dimensions: (1) physical health, (2) psychological health, (3) social relationships, and (4) environment (e.g., participation in and opportunities for recreation). In addition, two items are examined separately and involve individuals' overall perception of both their quality of life and health. Each of the 26 questions is rated on a 0-5 scale, and then summed to produce both a total score as well as domain-specific scores for more in depth analysis. Domain scores are scaled in a positive direction (i.e. higher scores denote higher quality of life). The mean score of items within each domain is used to calculate the domain score. Mean scores are then converted to range between 0-100 to enable comparisons to be made between domains comprised of unequal numbers of questions.

This quality of life instrument has been used in countless clinical investigations of pain, is validated specifically in postoperative populations following orthopedic surgery, and will increase the yield of this trial by improving comparisons with other investigations. This instrument has good clinical acceptability with minimal subject burden and is available in both self- and interviewer-administered formats. It has exceptional internal consistency, intra-rater (test-retest) reliability, construct validity, and discriminant validity.

UH3 Milestones. The 4-year UH3 implementation period has explicit milestones that are feasible, quantifiable, and scientifically justified to allow an assessment of progress. ***Annual milestones are listed below following the timeline (Table 4). All milestones must be completed in order to consider the UH3 definitive, pragmatic clinical trial successfully concluded.***

Table 4. Four-year **UH3** Implementation Phase pragmatic clinical trial **Timeline** (color added for clarity)

Funding Year:	**3**		**4**	**5**		**6**	
Months (within year):	**1-9**	**9-12**		**1-8**	**8-12**	**1-8**	**9-12**
Complete any revisions remaining from UG3 feasibility study	•						
Re-initiate subject enrollment	•						
Continue subject enrollment	•	•	•	•			
Data collection phone calls and database entry	•	•	•	•	•	•	
Medical Monitor reports (every 3 months)	•	•	•	•	•	•	•
DSMB reports (every 3 months)	•	•	•	•	•	•	•
Funding agency / oversight body reports (quarterly)		•	•		•		•
Enrolling center IRB Continuing Reviews		•	•	•	•	•	
Data entry and quality assurance		•	•	•	•	•	
Interim analyses (25%, 50%, 75% enrollment)		•	•	•			
Keep clinicaltrials.gov registry up-to-date		•	•	•	•	•	•
Data cleaning and analysis							•
Final data analysis							•

Results to coinvestigators and interpretation							•
Results sent to all study participants							•
Results sent to funding agency							•
Manuscript preparation and submission							•
Final results uploaded to clinicaltrials.gov							•
Study closure by all regulatory bodies							•
Conclude DSMB with final report							•
Final report to funding agency							•

Any revisions made to the feasibility study protocol and informed consent form (or any other aspect of the project) will have been completed during the last 2 quarters of the previous funding year (and submitted/approved by the appropriate regulatory bodies). Therefore, study staff already well versed in the logistics of the project will implement the protocol. As with the feasibility study, the Principal Investigator will review with the study team the entire first subject's course, from referral to enrollment to lead insertion to medical follow-up and adverse event or protocol deviation reporting for quality assurance. As with the feasibility study, prospective subjects will be identified in surgical clinics, referred to study personnel (adhering to HIPAA guidelines), offered enrollment by Research Coordinators, enrolled with written, informed consent, undergo the intervention and randomization, medical follow-up by the local Site Director, and data collection by the University of California San Diego.

Definitive information about the execution of the intervention will be collected by the Primary Investigator and provided to the funding agency (any deficiencies will be corrected with the Site Directors). As with the feasibility study, monitoring of all Sites will continue by the Primary Investigator, with quarterly reports provided to the Medical Monitor and DSBM, and to the funding agency / oversight body quarterly. The IRB continuing reviews will occur annually at the enrolling centers. Clinicaltrials.gov registry will remain up-to-date. We will continue to work closely with the NIH-DoD-VA Pain Management Collaboratory Coordinating Center regarding all aspects of the project.

Year 3 Milestones [Implementation Phase Year 1]:

- Revise protocol with approval by all regulatory bodies (HRPO and local IRBs)
- Re-initiate enrollment with revised protocol
- Successfully enroll approximately 20% of the total required enrollment
- Successfully collect and upload to the data-collection platform (database) all data from UH3 clinical trial subjects

Year 4 Milestones:

- Successfully enroll approximately 40% of the total required enrollment
- Successfully collect and upload to the data-collection platform (database) all data from UH3 clinical trial subjects
- First and second interim analyses after 25 and 50% of subjects enrolled, respectively
- Continuing approval by all regulatory bodies (DSMB, local IRBs, HRPO)

Year 5 Milestones:

- Successfully enroll the remaining required subjects to complete enrollment
- Successfully collect and upload to the data-collection platform (database) all data from UH3 clinical trial subjects
- Third interim analysis after 75% of subjects enrolled
- Continuing approval by all regulatory bodies (DSMB, local IRBs, HRPO)

Year 6 Milestones:

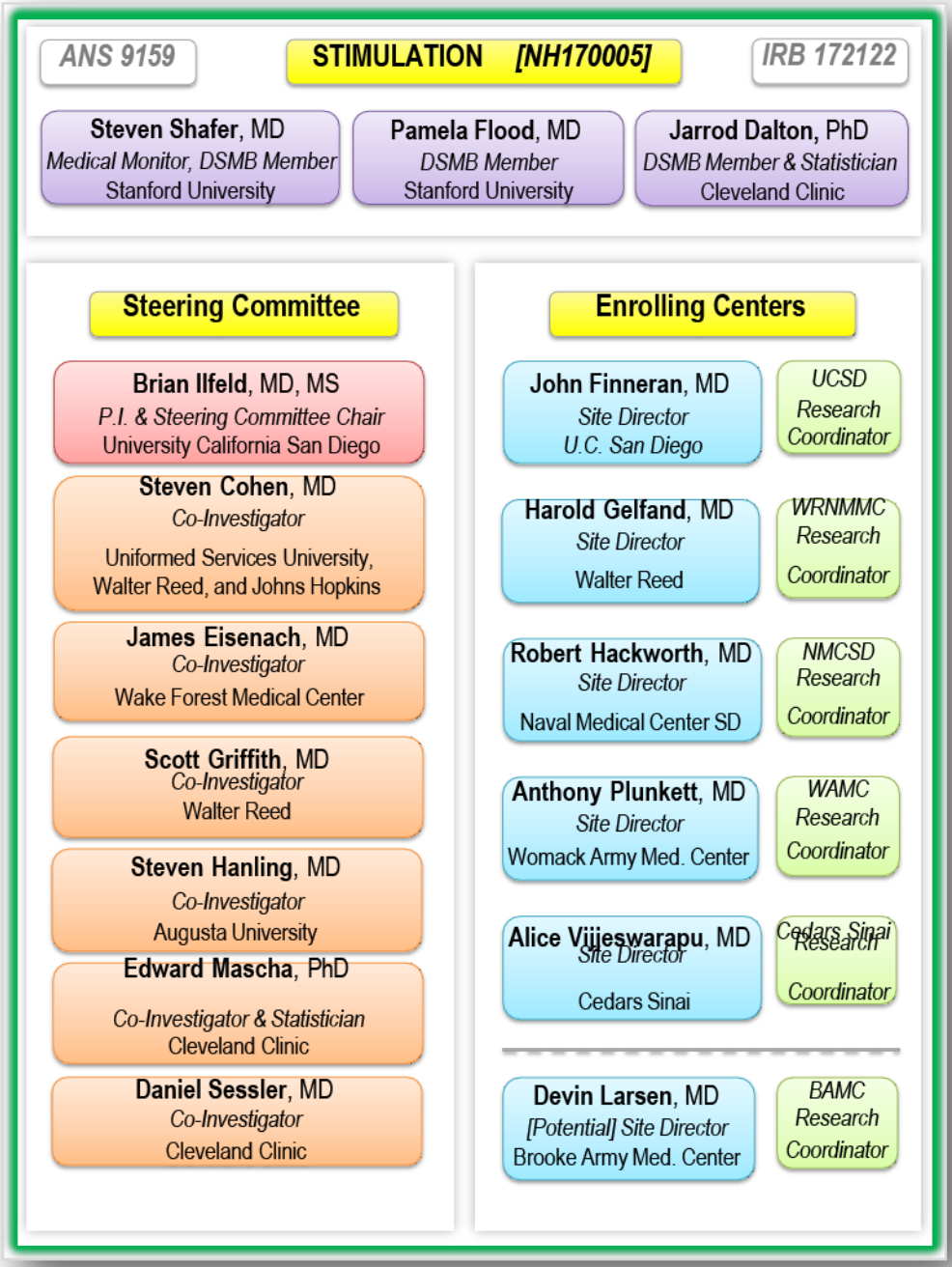
- Complete data collection 1 year following enrollment of the final subject (anticipated 3rd quarter)
- Successfully upload to the data-collection platform (database) final data
- Data cleaning and final analysis
- Results dissemination to coinvestigators and interpretation
- Results sent to funding agency and all study participants (by email or U.S. mail)
- Manuscript preparation and submission
- Clinicaltrials.gov updated with final results
- Study closure by all regulatory bodies (DSMB, local IRBs, HRPO)
- Conclude DSMB with final report
- Final report to funding agency

Medical Monitor. The study will have a designated medical monitor, Steven Shafer, MD, who will remain completely independent of the investigative team and will be a strong subject advocate. The Medical monitor 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.

Figure 12. Institutional projected quarterly enrollment, with the first year dedicated to regulatory approval, the second year for feasibility study enrollment and protocol revisions, 11 quarters of enrollment for the pragmatic clinical trial, a year for subject follow-up, and the final quarter for data analysis and manuscript preparation.

Ending May 15th of…	Year 1 (2019)				Year 2 (2020)				Year 3 (2021)				Year 4 (2022)				Year 5 (2023)				Year 6 (2024)				UG3	UH3	Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4			
BAMC									0	-	-	-	-	-	-	-	-	-	-	-					0	**0**	0
Cedars Sinai									1			3	9	9	9	9	9	9	9	9					1	**75**	76
NMCSD									1			1	3	3	3	3	3	3	3	3					1	**25**	26
UCSD			3	6	7	15	9	1	12	1		4	12	12	12	12	12	12	12	12					54	**100**	154
WRNMMC							3	0	0			1	3	3	3	3	3	3	3	3					3	**25**	28
WAMC									2			1	3	3	3	3	3	3	3	3					2	**25**	27
Quarterly Total	0	0	3	6	7	15	12	1	16	1	0	10	30	30	30	30	30	30	30	30	0	0	0	0	61	**250**	311
Yearly Total	9				35				27				120				120				0						

The Study Team (Figure 13). The study team consists of the Principal Investigator, 7 additional members of the Steering Committee, 6 Site Directors, and 1 research coordinator for each of the enrolling centers (Brooke Army Medical Center has regulatory approval to enroll subjects but lost the original Site Director due to an inter-base transfer; BAMC hopes to begin enrollment within the next year with a new Site Director).



Statistical Plan and Data Analysis [UG3 Phase]

Randomized groups will be compared for balance on baseline characteristics using descriptive statistics and the standardized difference (i.e., difference in means or proportions divided by pooled standard deviation). Absolute standardized differences larger than 0.487 (using formula in Austin 2009) will be considered imbalanced and the corresponding variables considered for adjustment in all analyses. Primary analyses will be modified intent-to-treat, such that all randomized patients who receive at least some of the study intervention will be included in the analyses. All patients who

receive at least some of the study intervention will be analyzed and in the group to which they were randomized.

Statistical methods will largely be the same for the Planning Phase (UG3) and the Implementation Phase (UH3). As explained below, one difference is that in the planning phase focus we will be on the estimated confidence interval for the treatment effects and the variability of the outcomes, as these will be used in designing the full trial. Another is that interim analyses and more thorough subgroup analyses will be done in the Implementation Phase. Details are given below.

For Specific Aim 2 we will estimate the treatment effect of PNS versus usual and customary care on pain and opioid consumption using a joint hypothesis testing framework. Specifically, we will conclude PNS is superior to usual and customary analgesia, at least one of Hypotheses 1 and 2 must be superior while the other either superior or at least noninferior.

We will first test for noninferiority of PNS to usual care on each of the two outcomes using 1-tailed noninferiority tests. The noninferiority deltas will be 1 point (worse) in pain score and 20% higher in opioid consumption. Noninferiority will be assessed at the overall 0.05 significance level with no adjustment to the significance criterion for testing two outcomes since noninferiority is required on both outcomes – i.e., an intersection union test. A noninferiority delta of 1 point in pain score is conservative since receiver operating characteristic curve analysis has demonstrated 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.[153,156,177-179]

We will assess noninferiority on pain score using a 1-tailed t-test which incorporates the noninferiority delta of 1 point. The estimated treatment effect for pain score will be derived from a linear mixed effects model with the outcome of patient's "average" pain score for each day (1,2,3,4,7), with fixed effects for intervention (PNS vs usual care), time (days 1 through 7) and assuming an autoregressive correlation structure among the measurements on the same patient over time. We will then test for noninferiority with a 1-tailed t-test in which the numerator is the estimated treatment effect from the model minus the noninferiority delta (1), and the denominator is the standard error of the estimated treatment effect. This method will yield results similar to comparing groups on the patient mean across these seven days but is more flexible since it allows for missing data and also directly accounts for the correlation within patient. The model also allows assessing the treatment-by-time interaction, but this will most likely not be of interest. As a sensitivity analysis we will relax the normality assumption and assess the treatment effect (plus test for noninferiority) on pain score over time using a mixed effects quantile regression model [1] in which we consider patient as a random effect, report the treatment effect as the difference in median pain scores, and use the same noninferiority delta of 1.

Cumulative opioid consumption is not typically normally distributed, but usually approximates a log-normal distribution. We therefore plan to assess the treatment effect of PNS versus usual care on the log transformed cumulative consumption from recovery room discharge through POD 7 using a simple linear regression model (equivalent to a t-test). The estimated treatment effect (i.e., difference between groups) will then be used in a noninferiority test with null and alternative hypotheses as: $H0: \mu1 - \mu2 \geq \log(1.2) = 0.263$ versus $HA: \mu1 - \mu2 < \log(1.2) = 0.263$, where $\mu1$ and $\mu2$ are the means of log-transformed opioid consumption for PNS and usual care, respectively, and $\mu1 - \mu2$ is estimated by the coefficient (i.e., beta) for PNS versus usual care in the regression model. The

estimated treatment effect beta will also be an estimate of the ratio of geometric means for the two groups, assuming data for each group is log-normal with similar coefficient of variation between groups.

In the planning phase, focus will be on the estimated confidence interval for the treatment effects and the variability of the outcomes.

Secondary outcomes will be assessed using appropriate statistical methods. We will use the t-test or Wilcoxon rank sum test for physical and functioning as measured by the Brief Pain Inventory (Hypothesis 3), chi-square analyses and t-test of Wilcoxon rank sum test for incidence and intensity of chronic pain, respectively (Hypothesis 4), and Wilcoxon rank sum for quality of life measure by the World Health Organization Quality of Life-BREF Instrument.

Subgroup analysis for sex. There is little relevant prior experience with the study intervention in the patient population of the proposed investigation, so it is not known whether either sex would interact with the treatment effect. Therefore, in accord with the Human Subjects recommendations, we will assess the treatment effect of PNS on each outcome of interest within sex subgroups. In addition, we will analyze each anatomic location to detect variations in treatment effect among the various lead insertion sites and types of surgical procedures. We will not require a significant interaction between treatment effect and these factors, but will rather conduct the subgroup analyses for each level of sufficient size (n=30). The subgroup analyses will be the same as those conducted on the entire sample, and so would be just as valid and unbiased.

Planning Phase (UG3) sample size considerations. The sample size for the planning phase of 64 patients will be sufficient to estimate the treatment effects of interest with moderate precision, i.e., a confidence interval width of roughly 1.1 standard deviations for each outcome measure. Confidence interval width for a standard deviation estimate will be 0.70 standard deviations. The planning phase will be sufficient to use in estimating the expected treatment effect and standard deviation for each outcome for the larger trial.

Missing outcomes data will be summarized along with a known etiology of the absence. While very little outcomes data is expected to be missing, all analyses will be intention to treat, and imputation of missing data using methods such an multiple imputation and last observation carried forward will therefore be utilized, based on the situation. We may also conduct a conservative analysis in which we assign the worst observed outcome to patients in intervention groups and best observed outcomes to those in control.

Throughout, the significance level will be 0.05 for each hypothesis. SAS statistical software (Cary, NC) will be used for all analyses, and East 6.0 (Cytel, Inc. Cambridge, MA) for interim monitoring and sample size calculations.

Statistical Plan and Data Analysis: Implementation Phase [UH3]

Randomized groups will be compared for balance on baseline characteristics using descriptive statistics and the standardized difference (i.e., difference in means or proportions divided by pooled standard deviation). Absolute standardized differences larger than 0.10 will be considered imbalanced and the corresponding variables considered for adjustment in all analyses.[2] Primary

analyses will be modified intent-to-treat, such that all randomized patients who receive at least some of the study intervention will be included in the analyses. All patients will be analyzed in the group to which they were randomized. Statistical methods for the Implementation Phase will generally follow the analyses conducted in the Pilot (UG3) phase.

Primary Aim. For Specific Aim 1 we will estimate the treatment effect of PNS versus usual and customary care on pain and opioid consumption using a joint hypothesis testing framework.[3] Specifically, we will conclude PNS is more effective than usual and customary analgesia if it is found to be superior on at least one of pain score or opioid consumption and not worse, i.e., noninferior, on both.

Noninferiority Testing. We will first test for noninferiority of PNS to usual care on each of the two outcomes using 1-tailed tests. The noninferiority deltas will be 1 point (worse) in pain score and 20% higher in opioid consumption. Noninferiority will be assessed at the overall (1-tailed) 0.025 significance level with no adjustment to the significance criterion for testing two outcomes since noninferiority is required on both outcomes – i.e., an intersection-union test. A noninferiority delta of 1 point in pain score is appropriate for between-group comparisons because it is about half the difference that would be considered clinically relevant for intra-subject changes: receiver operating characteristic curve analysis has demonstrated 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.[153,156,177-179]

We will assess noninferiority on pain score using a 1-tailed t-test which incorporates the noninferiority delta of 1 point. The estimated treatment effect for pain score will be derived from a linear mixed effects model with the outcome of patient's "average" pain score for each day (1,2,3,4,7), with fixed effects for intervention (PNS vs usual care), time (days 1 through 7) and baseline average pain score, and assuming an autoregressive (AR(1)) correlation structure among the measurements on the same patient over time. We will then test for noninferiority with a 1-tailed t-test in which the numerator is the estimated treatment effect from the model minus the noninferiority delta (1), and the denominator is the standard error of the estimated treatment effect.[4] This method will yield results similar to comparing groups on the patient mean across these seven days but is more flexible since it allows for missing data and also directly accounts for the correlation within patient. The model further allows assessing the treatment-by-time interaction, but this will be only of secondary clinical interest. As a sensitivity analysis we will relax the normality assumption and assess the treatment effect (plus test for noninferiority) on pain score over time using a mixed effects quantile regression model [1] in which we consider patient as a random effect, report the treatment effect as the difference in median pain scores, and use the same noninferiority delta of 1.

Cumulative opioid consumption is not typically normally distributed, and usually approximates a log-normal distribution, as in the pilot trial. We therefore plan to assess the treatment effect of PNS versus usual care on the log-transformed cumulative consumption through POD 7 using a linear regression model in which we adjust for any imbalanced baseline variables. The estimated treatment effect (i.e., difference between groups) will then be used in a noninferiority test with null and alternative hypotheses as: H0: $\mu 1 - \mu 2 \geq \log(1.2) = 0.263$ versus HA: $\mu 1 - \mu 2 < \log(1.2) = 0.263$, where $\mu 1$ and $\mu 2$ are the means of log-transformed opioid consumption for PNS and usual care, respectively, and $\mu 1 - \mu 2$ is estimated by the coefficient (i.e., beta) for PNS versus usual care in the regression model. The estimated treatment effect in the model will also be an estimate of the

ratio of geometric means for the two groups, assuming data for each group is log-normal with similar coefficient of variation between groups.

Superiority Testing. If noninferiority is found on both pain and opioid consumption we will test for superiority on each outcome using 1-tailed tests in the same direction. For superiority testing, since superiority on either outcome would be sufficient to reject the joint null hypothesis (i.e., a union-intersection test), we will control the type I error at 0.025 across the 2 outcomes by using a Bonferroni correction and using 0.025/2=0.0125 as the significance criterion.

Secondary Outcomes. We will assess the treatment effect on secondary outcomes using appropriate statistical methods. We will use a linear mixed effects model to assess the treatment effect over time for additional outcomes measured at days POD 1-7 (1, 2, 3, 4, 7), as in the primary analysis, including worst pain and the Defense and Veterans Pain Rating Scale; similarly we will assess the treatment effect on total severity score and total interference score at days 3 and 7. As sensitivity analyses we will also use a generalized ordinal regression model for each of these outcomes. For outcomes analyzed at a single time point (days 11, 18; months 1, 4, 12) we will use 2-sample t-test or Wilcoxon rank sum test for physical and functioning as measured by the Brief Pain Inventory (Hypothesis 3), chi-square analyses and t-test of Wilcoxon rank sum test for incidence and intensity of chronic pain, respectively (Hypothesis 4), and Wilcoxon rank sum test for quality of life measure by the World Health Organization Quality of Life-BREF Instrument. Analogous regression models would be used, as needed, to adjust for baseline imbalance.

Study-wide Type I error control. We will use a parallel gatekeeping procedure [1,5,6] to control the study-wide type I error at 0.05. For this procedure we *a priori* prioritize the study outcomes into 10 ordered sets, as given in **Table 5**. 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 0.025 [for each direction of interest; primary outcomes being 1-sided and all others 2-sided] 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 or Holm-Bonferroni correction) will be used as appropriate to control the type I error at the appropriate level.

Table 5. Ordered sets for Parallel Gatekeeping Procedure

Ordered Set #	Outcome(s)	Measurement Timing ^
1	Primary outcomes Average pain, opioid consumption	POD 1-7
2	Worst pain score	POD 1-7
	DVPRS	POD 1-7
3	BPI interference subscale	POD3, POD7
4	Worst pain	POD 1-11
	DVPRS	"
	Average pain	"
5	Worst pain	Months 4, and 12
6	Worst pain	POD 18
	DVPRS	"
	Average pain	"

7	Worst pain	Month 1
	DVPRS	"
	Average pain	"
8	Worst pain	Month 4
	DVPRS	"
	Average pain	"
9	BPI interference subscale	Months 1, 4, and 12
	WHO-DAS	"

* Additional outcome measures and time points, such as least and current pain levels (from the BPI) will be considered exploratory and not compared statistically

^ throughout, POD 1 refers to POD 0 after PACU through POD1

Assessment of treatment effect heterogeneity. There is little relevant prior experience with the study intervention in the patient population of the proposed investigation, so it is not known whether either sex would interact with the treatment effect. Therefore, in accord with the Human Subjects recommendations, we will assess the treatment effect of PNS on the primary outcomes of interest (pain score, opioid consumption) within levels of sex, and asses the interaction. In addition, we will assess treatment effect heterogeneity across within anatomical locations across the various lead insertion sites, across types of surgical procedures, and across levels of other baseline characteristics as listed below. We will assess the treatment-by-covariate interaction in the appropriate statistical model (i.e., the model used in the primary analyses). We will report the treatment effect within levels of each factor whether or not a significant interaction ($P<0.10$) is found.

We will assess treatment effect heterogeneity across levels of the following variables:

- sex (male, female)
- military (BAMC, WAMC, WRNMMC and NMCSD) vs. civilian (Cedars and UCSD)
- baseline average NRS (< 4, ≥ 4)
- baseline DVPRS (< 5, ≥ 5)
- baseline interference scale of the BPI < 20, ≥ 20)
- duration of surgery (< 90 min, ≥ 90 min)
- bupivacaine vs. ropivacaine (for the initial peripheral nerve block)
- saphenous nerve block (versus not) for lower extremity surgeries
- surgical site (shoulder, foot, ankle)
- surgical procedure (rotator cuff repair, hallux valgus, ankle arthrodesis, ankle arthroplasty)
- for brachial plexus leads: lead positioning (posterior to roots, superior trunk, middle trunk, other)
- for sciatic leads: lead positioning (medial, lateral)
- for sciatic leads: lead positioning (anterior, posterior)

Missing Data. While based on our UG3 results very little missing outcome data is expected, any missing data will be summarized overall and by randomized group along with the known/presumed etiology of the absence. If the missing data for an analysis appear to be missing at random for an outcome which is only designed to be measured once for a patient, we will assign values using multiple imputation (using 5 imputed datasets, and aggregating results across them) in which all other available baseline and outcome data will be used to predict the missing data point(s).[7] For longitudinal outcomes such as the primary outcome pain score, if data appear largely to be missing at random and with comparable frequency between groups, and all patients have at least some non-

missing data, we will ignore the missing data for the primary analysis. If there would be a non-trivial amount of missing data (e.g., > 10 percent missing) for a particular outcome, and the data did not appear in general to be missing at random, we would consider implementing a pattern mixture model approach in which randomized groups are compared on outcome within subgroups defined by the pattern of missing data, for e.g., with results then aggregated across patterns.

Interim Analyses for Efficacy and Futility. A substantive difference from the planning phase is that in the full trial we will conduct interim analyses to assess efficacy and futility at each 25% of the maximum planned enrollment. We will use a group sequential design with gamma spending function[8] and gamma parameters of -4 (quite conservative) for efficacy and -2 (moderately conservative) for futility (**Figure 14**). Assuming the alternative hypotheses were true, the probability of crossing a boundary for either efficacy (mainly) or futility at the first through fourth looks would be 0.07, 0.36, 0.75 and 1.0, respectively.

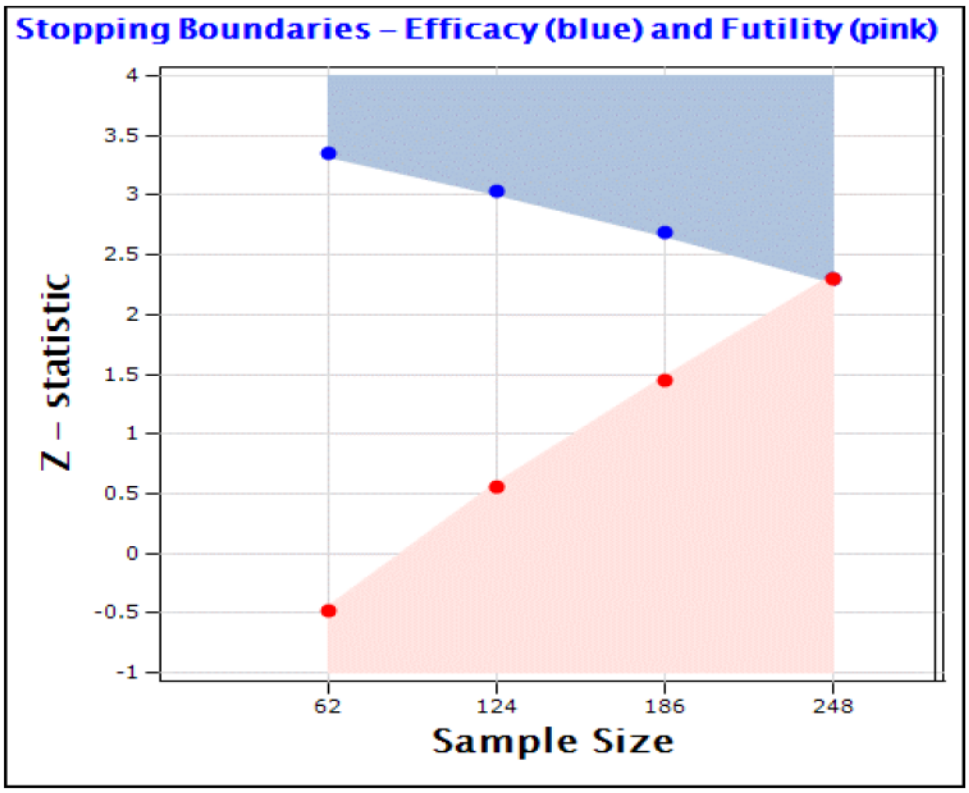


Figure 14. Stopping boundaries for 1-tailed tests for superiority for either pain score or opioid consumption. Blue region indicates superiority (reduced opioid consumption or pain score) and pink region indicates futility (lack of superiority). Z-statistic represents strength of evidence against the null hypothesis, either ratio of means or difference in means, each divided by standard error.

Sample size Justification and Considerations [UH3 Implementation Phase]. Sample size parameters for the implementation phase were informed from our estimates in the planning phase which included N=31 Stimulation and N=34 Placebo patients. For this full trial we choose a sample size which will maintain an overall 90% power at the 0.025 significance level (since 1-tailed tests) to claim the intervention more effective than the control on postoperative opioid requirements and pain

as measured by NRS pain score in our joint hypothesis testing framework. We plan the study to have 90% power to detect superiority on either outcome and at least noninferiority on both. Power for the joint hypothesis testing will be driven by superiority tests since superiority is needed for at least 1 of the 2 outcomes.

Opioid consumption. For cumulative opioid consumption through POD 7 our pilot study data had a coefficient of variation (CV) of 136% (mean (SD) of 17.9 ± 24.3 mg) for the Stimulation patients, 109% (mean (SD) of 17.9 ± 24.3 mg) for Placebo patients, and 142% (mean (SD) of 48 ± 68) overall. The ratio of geometric means (97.5% CI) in the pilot study was 0.20 (0.07, 0.57), for an 80% observed relative reduction, with confidence interval including as small as a 43% reduction.

For the implementation phase we conservatively assume a coefficient of variation of 150% for each group in opioid consumption through 7 days and plan for at least a 40% relative reduction. With these assumptions we will need a total of N= 228 patients to have 90% power to detect a relative reduction of 40% or more (i.e., ratio of geometric means of 0.60 or stronger) in mean opioid consumption at the overall 0.025 1-tailed significance level (0.0125 for each of the two 1-tailed tests for superiority). We use 1-tailed tests here because in the analysis we will only test for superiority after noninferiority of stimulation to placebo has been found. **After adjusting for interim analyses the required maximum total sample size is 250 (125 per group).**

With a sample size of 250 total we would further have 90% power to detect noninferiority in opioid consumption using a noninferiority delta of 1.2 for the ratio of geometric means after assuming a coefficient of variation of 150% and a true ratio of means of 0.75 or more. For a scenario with equal means (ratio of 1.0) we would only have about 25% power to detect noninferiority.

Pain score. In our pilot study we observed a reduction in the mean (97.5%CI) of average pain score of -1.7 (-2.5, -0.85) in Stimulation versus Placebo in the linear mixed effects model across POD1-7. We also observed a within-group standard deviation of pain score ranging from 1.1 to 2.6 across POD 1-7, and values of 1.1 for Stimulation and 1.7 for Placebo for the patient mean across those days. Finally, we observed an intraclass correlation of 0.47 for pain score in the linear mixed effects model across POD1-7. We used these estimates below in assessing the power and sample size for average pain score the implementation phase.

A difference between groups of 1.0 in average pain score is the smallest that would be considered clinically important. With a maximum total sample size of **250** we will have 95% power at the overall 0.025 1-tailed significance level (0.0125 for each of the two 1-tailed tests for superiority) to detect a difference of 1.0 or more between Stimulation and Placebo on mean pain score conservatively assuming a SD of 2.5 for pain score at each day (1, 2, 3, 4, 7) and ICC of 0.50.

Power for Subgroup Analyses. A main difference from the Planning/Pilot phase is that in this full trial we will have sufficient data to conduct the subgroup analyses and we also will have power to detect smaller treatment effects. For example, with 250 total patients, we would have about 90% power to detect a ratio of geometric means of 0.50 or stronger (smaller than observed in the pilot study) in subgroups of size N=125.

The overall significance level will be 0.025 for the primary aim when assessing noninferiority and superiority in 1-tailed tests, and 0.05 when assessing for superiority on secondary outcomes in both

directions. SAS statistical software (Cary, NC) will be used for all analyses, and East 6.0 (Cytel, Inc. Cambridge, MA) for interim monitoring and sample size calculations.

10. HUMAN SUBJECTS

Inclusion criteria: (1) Adult patients of at least 18 years of age; (2) with a planned single-injection peripheral nerve block(s); and (3) undergoing one of the following as a primary surgical procedure:

a. rotator cuff repair (shoulder)
b. ankle arthrodesis
c. ankle arthroplasty
d. hallux valgus correction ("bunionectomy" of the foot)

Exclusion criteria: (1) chronic opioid or tramadol use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks); (2) neuro-muscular deficit of the surgical limb; (3) compromised immune system based on medical history (e.g., immunosuppressive therapies such as chemotherapy, radiation, sepsis, infection), or other conditions that places the subject at increased risk; (4) implanted spinal cord stimulator, cardiac pacemaker/defibrillator, deep brain stimulator, or other implantable neurostimulator whose stimulus current pathway may overlap; (5) history of bleeding disorder; (6) antiplatelet or anticoagulation therapies other than aspirin due to the risk of bleeding with a 20-gauge insertion needle; (7) allergy to skin-contact materials (occlusive dressings, bandages, tape etc.); (8) incarceration; (9) pregnancy; (10) chronic pain of greater than 3 months in an anatomic location other than the surgical site; (11) anxiety disorder; (12) history of substance abuse; or (13) inability to contact the investigators during the treatment period, and vice versa (e.g., lack of telephone access).

For the initial pilot (UG3) study, to date 57 and 67 subjects have been enrolled at UC San Diego all centers combined, respectively (it is ongoing until we begin the UH3 definitive trial). For the definitive (UH3) study, anticipated enrollment at UCSD will be 125 subjects and anticipated enrollment at all other centers will be 125 subjects. Allowing for 83 additional subjects to account for drop-outs, the project at all enrolling centers for both UG3 and UH3 studies will enroll up to 400 subjects.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Enrollment. Surgeons, anesthesiologists or their counterparts (e.g., CRNAs, PAs) at each enrolling center will identify potential study subjects at preoperative patient visits prior to surgery. Surgeons will be seeing patients as part of regular medical care, and therefore this protocol will adhere to Health Insurance Portability and Accountability Act (HIPAA) regulations. Alternatively, the investigators may need to contact potential subjects prior to their pre-surgery visit and therefore request a waiver of consent for recruitment purposes. We will scan the upcoming ambulatory surgery schedule (which we have access to being anesthesiologists—we use this schedule daily for medical purposes), identify patients having the types of surgical procedures specified for this study, look in their electronic records to determine eligibility, and if eligible either call the potential subjects ourselves or provide the name and contact information to a research coordinator to contact the potential subjects.

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

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

3. This clinical trial could not be practicably carried out without the waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or, they are seen just 1-2 days prior to their date of surgery. We need to bring subjects into clinic within the 7 days prior to their surgery to have their leads inserted. We do not have enough time to do this the morning of surgery.

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

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

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

2. This clinical trial could not be practicably carried out without the waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or, they are seen just 1-2 days prior to their date of surgery. We need to bring subjects into clinic within the 7 days prior to their surgery to have their leads inserted. We do not have enough time to do this the morning of surgery.

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

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

Patients meeting inclusion and exclusion criteria will be presented with the study, and prospective study subjects desiring additional information will be required to give permission for a research coordinator to contact them to adhere to HIPAA requirements. The study protocol will be reviewed with interested prospective subjects in detail; and, for subjects desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or interventions. The

method of documenting consent will be using written informed consent forms approved by the local Institutional Review Board.

12. INFORMED CONSENT

Once a prospective subject contacts (or gives permission to be contacted by) an investigator or research coordinator by telephone or email, they will be provided information on the study purpose and protocol, as well as have any questions answered. Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled to arrive the day of surgery earlier than normal to allow for written informed consent and baseline instruments to be applied. Written informed consent will be attained prior to any measurements or procedures prior to surgery. Each site director is responsible for ensuring that written, informed consent is obtained from every subject at their respective enrolling center. Clinical research coordinators—also one for each enrolling site—will be specifically trained by the site directors to provide informed consent followed by documentation of informed consent using an Institutional Review Board-approved informed consent form. When subjects present for surgery, research coordinators will provide and attain written informed consent. This will occur in private patient care areas, so that subjects may feel comfortable asking questions of the research coordinator. If a subject desires—or if there is a question that a research coordinator cannot answer—the site director will be called in by the research coordinator to discuss the study directly with the subject.

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

This study protocol has follow-up data-collection telephone calls a maximum of 1 year following the initial study treatment, so repeated informed consent following the initial consent is unnecessary, as opposed to multi-year, longer-term clinical trials. Surrogate consent will not be accepted; therefore, if human subjects cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative is unacceptable for study enrollment.

13. ALTERNATIVES TO STUDY PARTICIPATION

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

14. POTENTIAL RISKS

The procedures and devices used in this study are already 510k cleared by the United States Food and Drug Administration to provide postoperative analgesia. However, there may be risks that are not yet known, and the incidences provided are all estimated with the exception of lead fracture. Potential risks include infection (<0.01% for up to 60 days of infusion),[5] lead fracture (7.5%), lead

dislodgement (<1%), nerve injury (<0.001%), bleeding (<0.01%), skin irritation (1-5%), lead migration (<0.1%), increased surgical pain, and discomfort/pain on insertion and/or during stimulation (10%).

In addition, there is the risk of loss of confidentiality. The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in locked medical offices and the locked Investigational Drug Service's files. Any digitized records containing personal health information will be stored as password-protected and encrypted files.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

The principle protection for participants and the true foundation for conducting a safe and effective clinical study is a well-trained and caring research staff. The principle investigator of this proposal, Dr. Brian Ilfeld, is an experienced multicenter clinical trial Principal Investigator with a Master of Science Degree in Clinical Investigation that included multiple classes specifically addressing the ethical conduct of human subjects research. Dr. Ilfeld has published special articles within peer-reviewed journals specifically addressing this issue (Ilfeld BM: Informed consent for medical research: an ethical imperative. *Reg Anesth Pain Med* 2006; 31: 353-7. PMID: 16857555). All study personnel will receive training in human subjects protection and compliance with the HIPAA regulations.

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). During stimulation, subjects will be contacted a minimum of once every 4 days by an investigator, 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 lead removal. This procedure has proven effective for ambulatory surgical patients with percutaneous peripheral nerve stimulation during the UG3 pilot study.

Precautions and responses to possible specific adverse events:

Infection: Leads will be placed under sterile conditions as is standard-of-care for any percutaneous device insertion. In addition, all patients having orthopedic surgical procedures receive perioperative antibiotics, which will further decrease any risk of infection. Subjects will be called daily and asked about signs and symptoms of lead infection. Should a lead become infected, it will be removed and oral antibiotics prescribed.

Lead fracture: It remains unknown what leads to lead fracture in a small percentage of patients, and therefore we cannot take specific steps to minimize its occurrence other than removing the leads with continuous, gentle traction.

Lead dislodgement and migration: Leads include a small "anchor" at the distal end to help keep the lead from withdrawing. In addition, the leads are shaped as a helical coil, which means they "unravel" if pulled on outside of the skin—the tip of the lead is withdrawn only after the entire lead has uncoiled with traction. Therefore, inadvertent dislodgement and migration are extremely unlikely. An occlusive dressing is used to affix the lead to the skin.

Nerve injury: Leads never intentionally come into contact with the nerve—they are inserted 0.5-2.0 cm distant from the target nerve. Therefore, a nerve injury should—theoretically—only occur with accidental contact with the target nerve. The investigators are all specifically trained and have experience inserting perineural catheters using ultrasound guidance, which permits real-time visualization of the insertion needle and target nerve.

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

Discomfort: Subjects will have a single-injection peripheral nerve block with long-acting local anesthetic prior to surgery and be provided with a prescription for an oral opioid. Therefore, if the electrical leads provide an inadequate degree of analgesia, subjects will take their oral opioids.

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

The study will have a designated medical monitor, Steven Shafer, MD, who will remain completely independent of the investigative team and will be a strong subject advocate. The Medical monitor 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.

The study Data Safety Monitoring Board (DSMB) will be comprised of the Medical Monitor, a physician experienced in both clinical trial management and the ethical conduct of research (Pamela Flood, MD), and a statistician, also well-experienced in multicenter trials (Jarrod Dalton, PhD). All three of these individuals will be completely independent of the investigative team. No member of the DSMB will have any financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. The board will comprise individuals with no vested interest in the outcome of the research study. The members will also sign a confidentiality statement. The DSMB will operate from a charter describing its role, membership, reporting procedures, and meeting protocol. The DSMB will decide on its own protocols, set triggers for data review or analyses, and establish guidelines for monitoring the study, stopping the study for safety concerns, and for efficacy based on plans specified in the protocol. Confidentiality will be maintained during all phases of DSMB review and deliberations. DSMB members will maintain strict confidentiality concerning all privileged trial results provided to them. The board will perform the following functions:

• Approval of the trial protocol before enrollment of patients

- Review the data in order to determine efficacy, futility, and safety, and to determine whether the study should continue
- Review data quality and data integrity
- Evaluate risk versus benefit by thorough examination of the data accumulated
- Determine whether the trial is proceeding as planned, the protocol is being followed, the recruitment of patients is on schedule, and data are being collected with the proper accuracy
- Review patient dropouts, if any, and make appropriate recommendations
- Determine whether safety concerns have been raised by the experimental or control treatments

Review Items. Items to be reviewed by the DSMB include:
- Interim/cumulative data for evidence of study-related adverse events
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines in the study protocol
- Data quality, completeness, and timeliness
- Performance of individual centers
- Adequacy of compliance with goals for recruitment and retention, including those related to participation of women and minorities
- Adherence to the protocol
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations etc.)
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study

Recommendations. The DSMB will conclude each review with their recommendations to the principal investigator and primary site Institutional Review Board (at the University of California San Diego) as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study may include:
- Modifications of the study protocol based upon the review of the safety data
- Suspension or early termination of the study or of one or more study arms because of serious concerns about patients' safety, inadequate performance, or rate of enrollment
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines
- Optional approaches for executive committee and investigators to consider when the DSMB determines that the incidence of the primary study outcomes is substantially less than expected, such as recommendations to increase the number of trial centers or extend the recruitment period
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious

Appropriate reports will be made to the Institutional Review Boards at all enrolling centers and the executive committee, comprised of all co-investigators and site directors

Patient Serious Adverse Event Reporting. All unanticipated events and adverse events will be reported to the specific center's Institutional Review Board (IRB), the primary supervising IRB (University of California San Diego), the study Data and Safety Monitoring Board (DSMB), and the Army Human Research Protections Office. The adverse event and unanticipated event profile will be discussed at monthly executive committee video-conference meetings.

Management of adverse events. Adverse events for study-related injuries will be managed by the site director of each center. For a medical emergency that is potentially life-threatening, subjects will

be instructed to dial 911 for emergency services to go directly to their location, and the site director will meet the subject at the site's emergency department.

In the event of a study-related injury, the treatment institutions will provide medical care needed to treat those injuries without cost to study subjects. The institutions will not provide any other form of compensation for study-related injuries. This information is specified within the informed consent forms. The forms also instruct subjects to contact the local Institutional Review Board, the enrolling investigator, or the principal investigator of the study for further information (phone numbers provided for all entities). In addition, active duty United States Armed Forces service members who enrolled at a civilian institution who sustain a research-related injury may receive medical care at a military hospital or clinic free of charge. The informed consent form instructs active duty service members to contact the United States Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) for issues that are inadequately resolved (with phone number).

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Pre-ICF information. The only information that will be recorded on hard-copy format before a subject provides written, informed consent is date of surgery, surgeon, name, contact phone numbers, and email address. This information will be destroyed using a paper shredder (or in the locked UCSD PHI disposal stations) following contact with the patient. If the patient does not participate, then there will be no record of PHI whatsoever.

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.

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

Subjects might experience less postoperative pain than they otherwise would have without participation. If so, they might require fewer opioid analgesics and have a lower risk of experiencing opioid-related side effects such as nausea, vomiting, and pruritus. They might have a lower risk of chronic pain, opioid dependence, and mental/physical disability.

18. RISK/BENEFIT RATIO

While there are risks involved in the insertion, use, and removal of percutaneous leads, they are relatively rare and not catastrophic when they do occur. With its ease of insertion, prolonged duration of action, presumably lower risk of complications or side effects, and simple removal, neuromodulation has the very real possibility of replacing local anesthetic administration—the standard of care for the past 100 years—that would completely revolutionize postoperative analgesia, as we know it.

19. EXPENSE TO PARTICIPANT

There will be no additional costs to subjects as a result of being in this study, other than any transportation costs and parking charges for their return trip for lead removal. If a subject is injured as a direct result of participation in this research, the University of California will provide any medical care they need to treat those injuries. The University will not provide any other form of compensation for an injury.

20. COMPENSATION FOR PARTICIPATION

There is no compensation for participation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator, **Brian M. Ilfeld, MD, MS,** is a board-certified anesthesiologist with fellowship training in and 19 post-training years experience with regional anesthesia and acute pain medicine. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC Medical Centers. Dr. Ilfeld, or another investigator, will follow all subjects following their treatment. Dr. Ilfeld will be responsible for the overall management of this study, as well as for the well-being of study subjects.

Co-investigators, **John Finneran, MD**; **Engy Said, MD; Rodney Gabriel, MD, MAS; and Matthew Swisher, MD;** are board-certified anesthesiologists with fellowship training in and extensive experience with regional anesthesia and acute pain medicine. All hold a license to practice medicine in California and have medical privileges at the UC Medical Centers. All will help consent subjects, perform a history and physical exam, perform the treatment on subjects, and will follow subjects following their treatment.

The study will be overseen a medical monitor, **Steven Shafer, MD**, of Stanford University, Stanford, California—in essence a study subject advocate. As the former Editor-in-Chief of one of anesthesiology's two highest-impact medical journals, a clinician, and a Federally-funded research himself, Dr. Shafer is thoroughly experienced in management of clinical trials, the ethical conduct of clinical research, the patient population under investigation, and Acute Pain Medicine interventions for postoperative analgesia. As such, Dr. Shafer is a strong study subject advocate. Dr. Shafer has extensive experience working on committees and authoring/editing peer-reviewed evidence-based publications, and will be an active member of the DSMB. He has been, and will continue to be, completely independent of the investigative team. In addition, Dr. Shafer has no financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Lastly, he has no vested interest in the outcome of the research study. Dr. Shafer will remain completely independent of the investigative team and will be a strong subject advocate. The Medical monitor 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.

DSMB members Pamela Flood, MD, and Jarrod Dalton, PhD, are from Stanford University and the Cleveland Clinic, respectively. Dr. Flood is a board-certified anesthesiologist and clinical researcher in the with extensive experience involving the ethics of human subjects research. Dr. Dalton is a statistician with 15 years of experience involving clinical research.

Baharin Abdullah is a project manager with the UCSD Department of Anesthesiology; and **Jeffrey Mills** is a research coordinator with the UCSD CTRI. Both individuals have the required training—including up-to-date CITI training—for their positions.

22. BIBLIOGRAPHY

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23. FUNDING SUPPORT FOR THIS STUDY

Drs. Ilfeld and Finneran will be supported by a Department of Defense grant award (NH170005) which will help to support his nonclinical time and the product used in this investigation. Start date for this grant was May 15, 2018 and will terminate after 6 years. Please contact Yolanda Boyd, grants specialist, at (619) 471-3320 for information regarding this DoD grant. All funding for this investigation is provided by the Department of Defense.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT

Not applicable.

25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER

Not applicable.

26. IMPACT ON STAFF

None. All study procedures will be executed by investigators and research coordinators without the assistance of non-investigator staff members.

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

None.

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

Not applicable: surrogate consent will not be accepted.

Revised Protocol

Dated May 2021, following enrollment of the first participant

UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN

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

Version date: 9/30/2013

1. PROJECT TITLE

Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain

2. PRINCIPAL INVESTIGATOR

Brian M. Ilfeld, MD, MS

3. FACILITIES

UCSD hospitals and the UCSD CTRI

4. ESTIMATED DURATION OF THE STUDY

Six years (1 year regulatory and preparation, 3.5 years enrollment, 1 year follow-up, 0.5 year analysis and publication)

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

Postoperative pain is usually treated with opioids that have undesirable and sometimes dangerous side effects (e.g., vomiting and respiratory depression)—and yet over 80% of patients still experience inadequate pain relief. A novel, non-pharmacologic analgesic technique—percutaneous peripheral nerve stimulation (PNS)— holds extraordinary potential to greatly reduce or obviate opioid requirements and concurrently improve analgesia following painful surgery. This technique involves inserting an insulated electric lead adjacent to a target nerve through a needle prior to surgery using ultrasound guidance. Following surgery, a tiny electric current is delivered to the nerve resulting in potent pain control without any cognitive or adverse systemic side effects whatsoever. The electrical pulse generator (stimulator) is so small it is simply affixed to the patient's skin. The leads are already cleared by the US Food and Drug Administration to treat acute (postoperative) pain for up to 60 days; and, since percutaneous PNS may be provided on an outpatient basis, the technique holds the promise of providing potent analgesia outlasting the pain of surgery—in other words, the possibility of a painless, opioid-free recovery following surgery. We propose a multicenter, randomized, quadruple-masked, placebo-controlled, parallel-arm clinical trial to determine the effect of percutaneous PNS on postoperative analgesia and opioid requirements, as well as physical and emotional functioning, the development of chronic pain, and ongoing quality of life. This investigation has a strong potential to dramatically reduce or obviate postoperative opioid requirements and their resultant negative effects on both individuals and society; while concurrently improving analgesia, increasing the ability to function in daily life, decreasing the risk of transition from acute to chronic pain, and improving quality of life.

6. SPECIFIC AIMS

UG3 Planning Phase

The initial UG3 feasibility study will be a randomized, double-masked, placebo-controlled, parallel-arm, human subjects pilot study with two Specific Aims:

Specific Aim 1 (UG3): To determine the **feasibility** and **optimize** the protocol of the Implementation Phase (UH3) multicenter clinical trial that will compare percutaneous PNS with usual and customary opioid-based analgesia following moderate-to-severely painful ambulatory surgery.

Specific Aim 2 (UG3): To ***estimate*** the **treatment effect** of percutaneous PNS on pain and opioid consumption following moderate-to-severely painful ambulatory surgery compared with usual and customary opioid-based analgesia. This will allow determination of the required **sample size** of the definitive multicenter clinical trial of the Implementation Phase (UH3).

UH3 Implementation Phase

The primary Specific Aim of the trial is to determine the effect of percutaneous PNS on postoperative **opioid** requirements and **analgesia** following moderate-to-severely-painful ambulatory surgery (under the usual conditions in which PNS will be applied, making this a "pragmatic trial"). Secondary Specific Aims are to determine the effect of percutaneous PNS on physical and emotional **functioning**, **chronic pain**, and **quality of life** following moderate-to-severely-painful ambulatory surgery.

Hypothesis 1 (UH3)*:* **Opioid** consumption will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia (measured in oral morphine equivalents).

Hypothesis 2 (UH3): Surgical **pain** will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Hypothesis 3 (UH3)*:* Physical and emotional **dysfunction** due to pain will be decreased in the 12 months following ambulatory surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the Brief Pain Inventory).

Hypothesis 4 (UH3)*:* The incidence and intensity of **chronic pain** will be decreased 4 and 12 months following surgery with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Hypothesis 5 (UH3)*:* **Quality of life** will be improved 1,4 and 12 months following surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the World Health Organization Quality of Life-BREF Instrument).

7. BACKGROUND AND SIGNIFICANCE

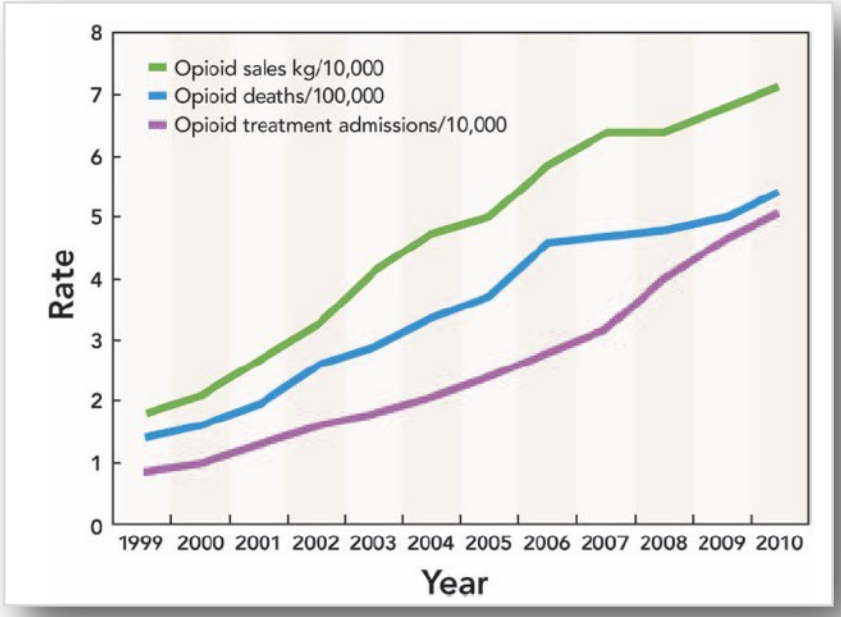
Background. There are tens-of-millions of ambulatory surgical procedures performed in the United States annually. Over 80% of patients experience inadequate pain relief following surgery with

consequences for both individuals and society. For patients, inadequate postoperative analgesia results not only in suffering, but also an increased risk of comorbidity (e.g., perioperative myocardial infarction), inferior rehabilitation, and the transition from acute pain to persistent ("chronic") post-surgical pain [incidence: 10-50%]. Persistent post-surgical pain frequently results in decreased productivity and a strain on personal relationships, as well as an increased risk of depression, chronic low-back and joint pain, obesity, and accelerated onset of cardiovascular disease. For society as a whole, inadequately-treated acute pain is a burden to the healthcare system, requiring increased healthcare provider time and the costs of readmission for ambulatory patients. Furthermore, persistent post-surgical pain not only increases medical care costs, but decreases overall economic output: the economic toll for chronic nonmalignant pain is over $100-billion annually within the United States.

Clearly, inadequately-controlled post-surgical pain is a substantial problem, which is intimately related to a reliance on perioperative opioids use—the foundation of postoperative analgesia for over a century. Unfortunately, opioids have significant undesirable consequences for both individuals and society. Frequent systemic side effects such as nausea, vomiting, and pruritus are irritants; but some effects may be fatal, such as cognitive impairment[13] and respiratory depression (with life-threatening hypoventilation requiring naloxone administration occurring in 1 of 333 patients). And, even minor ambulatory surgical procedures can lead to chronic opioid use, with significant negative consequences such as hyperalgesia, dependence and decreased quality of life.

The toll of opioids on society cannot be overemphasized. In the last 20 years the rate of prescription opioid diversion, abuse, addiction, and overdose has multiplied dramatically (**Figure 1**), with the overall economic cost of opioid abuse within the United States in excess of $70-billion annually. Over 5-million people within the United States use prescription analgesics without medical need or prescription, and this rate has more than doubled in the last 20 years. In excess of 28,000 deaths due to overdose occurred within the United States in 2010, a 700% increase in less than 2 decades. Shockingly, 65-80% of current heroin-dependent users began their addiction by abusing prescription opioids.

Figure 1. Rates of opioid analgesic sales, unintentional overdose deaths, and addiction treatment admissions.[1]



Considering ***4-20% of all opioid pills prescribed within the United States are diverted and abused—almost 500-million doses annually***—the supply of oral opioids is of great concern. Nearly 80% of abused oral opioids were originally intended for someone else, with most obtained from a friend or relative. Unused prescription opioids are so ubiquitous that "young recreational

users do not have to venture outside their immediate social networks to find those who will sell or share pills." Indeed, it has been conclusively demonstrated that both the abuse of opioids and extent of diversion are relative to their prescriptive availability.

Wounded service members and Veterans have been disproportionately affected, given that addiction is especially common in populations with co-existing psychopathology (e.g., depression, post-traumatic stress disorder). 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. Within the U.S. Armed Services, the most-commonly abused class of prescription drugs is opioids, ***with the incidence of prescription drug misuse increasing from 2% to 11% between 2002 and 2008.*** 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 to what most now describe as an epidemic. The Department of Defense has prioritized non-addictive analgesic modalities for pain states that are currently treated primarily with opioids. Thus, inadequately-controlled postoperative pain and opioid diversion/abuse are significant challenges for Armed Services members, Veterans and their families. A new treatment for postoperative pain is desperately needed to both improve analgesia and concurrently decrease dependence on opioids.

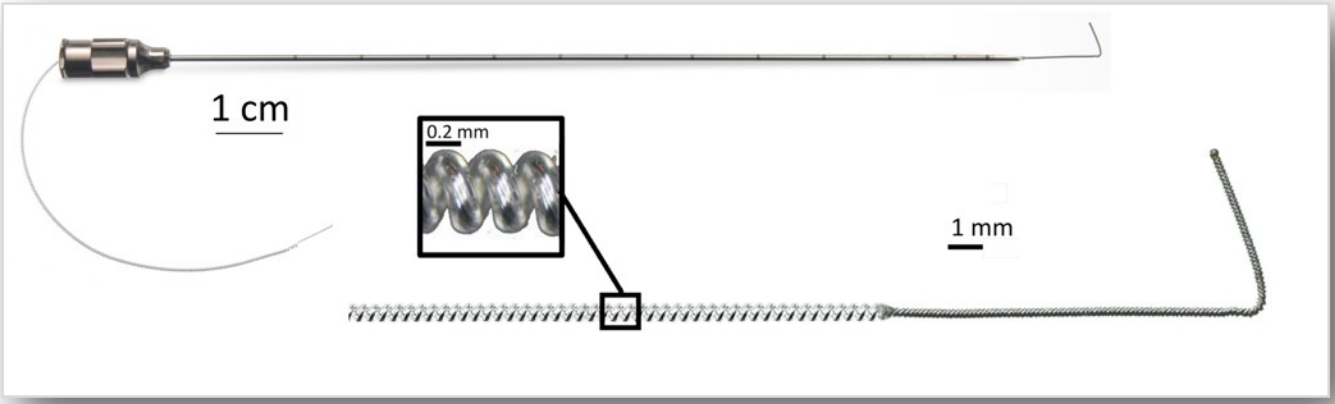
One analgesic alternative—**percutaneous peripheral nerve stimulation (PNS)**—holds extraordinary promise to improve post-surgical analgesia while concurrently decreasing or obviating opioid requirements; and, all without any adverse systemic side effects.

Many hypotheses have been proposed to explain the analgesic effects of stimulation—also termed "***neuromodulation***", but Melzack and Wall's "gate control theory" is the most common and accepted theory: electric current stimulates large-diameter afferent peripheral nerves that subsequently interrupt communication (the "gate") from small-diameter pain fibers to the central nervous system at the level of the spinal cord. Neuromodulation has a long history—and demonstrated efficacy—in the management of ***chronic*** pain using surgically implanted spinal cord and peripheral nerve stimulators.

However, the application of neurostimulation to ***postoperative*** pain states has been limited by the invasive nature of the available electrical leads: conventional units typically require multiple electrodes in close proximity to the peripheral nerve that require invasive and time consuming surgery to place and subsequently remove. Stimulation with electrodes placed on the skin (transcutaneous electrical nerve stimulation, "TENS") has been investigated previously to determine if it has the potential to avoid these limitations. However, activation of pain fibers in the skin greatly limit the degree of tolerated current that can be delivered by TENS and creates an undesirable analgesic 'ceiling'.

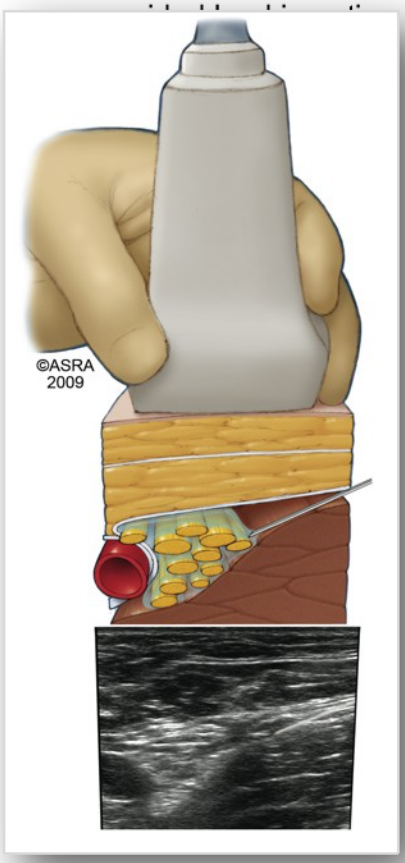
To apply neurostimulation to treatment postoperative pain, optimally this modality should be administered without an open surgical incision. ***Extremely small, insulated electrical leads have now been developed that permit relatively rapid percutaneous insertion through a needle***, obviating the need for a surgical incision (**Figure 2**, following page; MicroLead, SPR Therapeutics, Cleveland, OH).[1]

Figure 2. A 12 cm, 20 g needle with a pre-loaded helically-coiled insulated electrical lead (inset: a magnified lead).



Using ultrasound to guide placement, a lead may be reliably inserted 0.5-3.0 cm from a peripheral nerve using similar landmarks and accepted approaches as for peripheral nerve block or perineural catheter administration (**Figure 3**).

Figure 3. Ultrasound-



An external stimulator—so small that it may be directly adhered to the skin (**Figure 4**)—subsequently delivers a small electric current through the insulated lead to the target nerve.

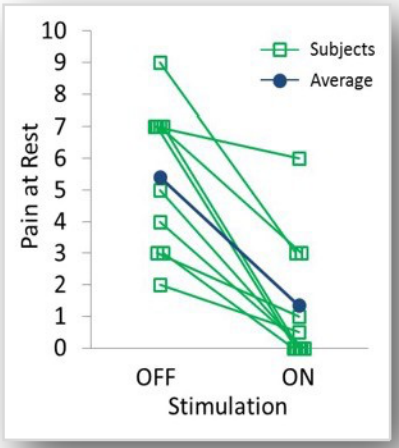
Figure 4. A stimulator (inset) and setup for percutaneous peripheral nerve stimulation



Preliminary studies and pilot data. We recently published 2 series of cases describing the first uses of percutaneous PNS to treat postoperative pain [funded, in part, by NIH 1R44AG052196].[1,2] We used the novel leads described previously that were recently cleared by the US Food and Drug Administration (FDA) to treat acute pain within the peripheral nervous system. A total of 10

individuals were included who experienced pain difficult to control with oral analgesics between 6 and 97 days following total knee arthroplasty. Using ultrasound guidance, a femoral and/or sciatic nerve electrical lead was inserted, depending on where the majority of pain originated (anterior vs. posterior knee, respectively). Pain scores were recorded before and after the stimulator was activated. ***Of these 10 subjects, 5 had complete resolution of their pain, 4 experienced a 57-67% decrease, and 1 a 14% reduction (Figure 5).***[1,2]

Figure 5. Pilot data



The significant analgesia demonstrated in these 10 subjects led our group to investigate the possibility of using PNS immediately following surgery. Seven patients had femoral and sciatic nerve leads inserted using ultrasound guidance prior to undergoing total knee arthroplasty.[3] A single-injection adductor canal nerve block was administered using a long-acting local anesthetic, and surgical anesthesia provided with a spinal or general. The following morning stimulators were reconnected to the leads and current delivered continuously for up to 6 weeks. Patients were discharged home with their leads *in situ*. In 6 of 7 subjects (86%), the average of daily pain scores across the first 2 weeks was well controlled and mild (<4 on the 0-10 Numeric Rating Scale for pain). Of the 5 subjects with data on opioid use, ***the median time to complete opioid cessation was only 8 days, with 100% of subjects opioid-free 1 month following surgery.*** This is a dramatic improvement compared with the typical median time to cessation of nearly 2 months (vs. 8 days), with a 1-month opioid-independence rate of 11-33% (vs. 100%) for patients having the same surgical procedure within the United States.

The opioid-sparing potential of PNS for painful ambulatory surgery is illustrated by one subject who, following a hallux valgus repair ("bunionectomy")—one of the most painful orthopedic procedures performed—reported only mild pain and **required no opioids** from the recovery room through her entire period of convalescence with two weeks of sciatic nerve stimulation (unpublished data). Due to the ability to provide PNS in ambulatory patients and a treatment duration of up to 30 days, the PNS system outlasted the pain of surgery. These remarkable results led our team to submit an application to the Department of Defense (FY16 Peer Reviewed Orthopaedic Research Program) to support a clinical trial investigating the use of percutaneous PNS to improve function and rehabilitation following orthopedic **trauma** of the lower extremity using knee arthroplasty as a model.

Significance. In contrast to that submission and our previous work involving inpatient knee arthroplasty, the present application proposes applying percutaneous PNS to the most painful ***ambulatory*** surgical procedures to improve postoperative analgesia and dramatically reduce opioid requirements. If successful, benefits of ***decreasing pain in the immediate postoperative period*** may lead to a plethora of patient benefits beyond simply decreasing suffering and opioid requirements, including decreasing pain-related interference in activities of daily living and greatly improving physical rehabilitation—in and of itself critical in maximizing long-term outcomes. In addition, persistent post-surgical pain is correlated with increased perioperative pain; and, therefore, maximizing postoperative analgesia may decrease the incidence of transition from acute to chronic pain [incidence: 10-50%], reduce pain-related interference in activities of daily living, and improve quality of life.

Moreover, greatly reducing opioid requirements will not only reduce irritating systemic side effects such as nausea, vomiting, and pruritus; but diminish the incidence and severity of cognitive impairment and respiratory depression (with its associated mortality). Crucially, if opioid requirements can be dramatically reduced—or even eliminated—for the most painful ambulatory surgery, then opioid prescriptions may be drastically reduced or even eliminated for all related surgical procedures associated with a lower degree of pain. It is imperative that novel, non-opioid postoperative analgesic modalities are developed and disseminated considering:

- Tens-of-millions of ambulatory procedures are performed annually
- The number of surgical procedures is expected to grow exponentially in the coming decades
- Up to 20% of prescribed opioids—almost 500-million doses annually—are diverted and abused
- The abuse of opioids and extent of diversion are relative to their prescriptive availability
- Illicit opioid use has grown to epidemic proportions
- U.S. military personnel, Veterans and their families are disproportionately affected by these catastrophic trends with the incidence of prescription drug misuse increasing from 2% to 11% in the six years leading to 2008, and this trend continues unabated.

Ultrasound-guided percutaneous PNS has been used to treat chronic pain (e.g., phantom limb pain),[4] has demonstrated extraordinary potential to provide potent postoperative analgesia and concurrently reduce opioid requirements in our pilot studies, and is already cleared by the US FDA for use in treating post-surgical pain. Most importantly—and in contrast to opioids—***it has no abuse/addiction potential, produces no adverse systemic side effects, and does not influence cognitive functioning whatsoever.***[4] Consequently, we propose an initial pilot study phase (UG3) followed by a definitive randomized, quadruple-masked, placebo-controlled, parallel design, human subjects pragmatic clinical trial to determine the effect(s) of ultrasound-guided, percutaneous PNS on postoperative **pain, opioid requirements,** and **functioning/quality of life** following painful ambulatory surgical procedures.

8. PROGRESS REPORT

The pilot study (UG3) results: Cumulative opioid consumption for the first 7 postoperative days for the stimulation group (n=31) was a median [IQR] of 5 [0,30] versus 48 [25,90] mg for the sham group (n=34), ratio of means 0.20 (0.08, 0.50); P<0.001). Patient average pain score over the first 7 days for the stimulation group was a mean (SD) of 1.1 (1.4) vs. 3.1 (2.3) for the sham group, difference in means (95% CI) of -1.7 (-2.4, -1), P<0.001).

9. RESEARCH DESIGN AND METHODS

We propose a ***feasibility study*** during the initial 2-year Planning Phase [UG3] and multicenter, randomized, quadruple-masked (investigators, subjects, statisticians, manuscript authors), placebo-controlled, parallel arm, human-subjects ***pragmatic clinical trial*** period during the subsequent 4-year Implementation Phase [UH3] to determine if ultrasound-guided percutaneous peripheral nerve stimulation (PNS) greatly reduces or obviates postoperative opioid requirements while concurrently decreasing surgical pain. For the entire duration of the funding period we will comply with policies and practices developed by the Work Groups of the NIH-DoD-VA Pain Management Collaboratory, and we will work with the Coordinating Center in providing relevant information and material. We have included a diverse group of recruitment sites that will provide a broad, representative patient sample of active duty military members and their families. Study participants will be recruited from 6

centers, including both U.S. military and civilian medical centers within a wide geographic range, providing a study sample with ethnic, racial, and socioeconomic diversity.

U.S. military medical centers:

- Brooke Army Medical Center [San Antonio, Texas]
- Fort Bragg [Fayetteville, North Carolina]
- Naval Medical Center San Diego [San Diego, California]
- Walter Reed National Military Medical Center [Bethesda, Maryland]

Civilian university medical centers:

- University California San Diego [San Diego, California]
- Cedars Sinai [Los Angeles, California]

The study protocol and materials will be approved by each center's Institutional Review Board; and, the investigation will be prospectively registered on the clinicaltrial.gov website. The study will be overseen by a Data Safety Monitoring Board comprised of two physicians familiar with the ethical conduct of clinical research and one biostatistician. The DSMB will review enrollment, study data, protocol violations, adverse events, and oversee all aspects of the clinical trial.

UG3 Planning Phase

The initial UG3 feasibility study will be a randomized, double-masked, placebo-controlled, parallel-arm, human subjects pilot study with two Specific Aims:

Specific Aim 1 (UG3): To determine the **feasibility** and **optimize** the protocol of the Implementation Phase (UH3) multicenter clinical trial that will compare percutaneous PNS with usual and customary opioid-based analgesia following moderate-to-severely painful ambulatory surgery.

Specific Aim 2 (UG3): To ***estimate*** the **treatment effect** of percutaneous PNS on pain and opioid consumption following moderate-to-severely painful ambulatory surgery compared with usual and customary opioid-based analgesia. This will allow determination of the required **sample size** of the definitive multicenter clinical trial of the Implementation Phase (UH3).

Therefore, the protocol for the UG3 Planning Phase feasibility study and the UH3 Implementation Phase pragmatic trial will be identical, with the exception of any improvements determined by the UG3 study.

Enrollment. Surgeons at each enrolling center will identify potential study subjects at preoperative patient visits. Surgeons will be seeing patients as part of regular medical care, and therefore this protocol will adhere to Health Insurance Portability and Accountability Act (HIPAA) regulations. Patients meeting inclusion and exclusion criteria will be presented with the study, and prospective study subjects desiring additional information will be required to give permission for a research coordinator to contact them to adhere to HIPAA requirements. Research coordinators will review the study protocol in detail with interested prospective subjects; and, for subjects desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or

interventions. The method of documenting consent will be using written informed consent forms approved by the local Institutional Review Board.

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 [this is standard for the surgery regardless of study participation]. 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 until lead removal. Anthropomorphic and demographic characteristics as well as baseline end points will be recorded/measured.

Table 1. Anatomic locations for electrical leads and peripheral nerve blocks.

Surgical Location	Surgical Procedures	Lead Location	Peripheral Nerve Block Location
Shoulder	• Rotator cuff repair	Brachial plexus roots/trunks	Brachial plexus roots/trunks
Foot or ankle	• Hallux valgus correction • Ankle arthrodesis or arthroplasty	Sciatic	Popliteal sciatic [saphenous nerve block optional]

Lead insertion. Intravenous fentanyl (0-100 µg) and/or midazolam (0-2 mg) may be administered for patient comfort. Insulated leads will be inserted prior to peripheral nerve block administration. The lead insertion sites will be cleansed with chlorhexidine gluconate and isopropyl alcohol, and a sterile, fenestrated drape applied. A portable ultrasound paired with either a linear or curved array transducer within a sterile sleeve will be used for lead insertion (**Figure 9**). The target nerve will be imaged in a transverse cross-sectional (short axis) view and a local anesthetic skin wheal raised lateral to the ultrasound transducer.

Figure 9. Ultrasound-guided sciatic nerve lead insertion



Using an in-plane ultrasound guidance, we will implant approximately 1-2 cm from the target nerve a pre-loaded, monopolar, helically coiled, insulated lead (SPR Therapeutics, Cleveland, OH) attached to an external pulse generator (SPR Therapeutics) with a surface return electrode. Accurate lead placement will be confirmed with subject reports of comfortable sensations over the surgical site without eliciting muscle contractions.

Frequency will be set to 100 Hz, which is known to generate comfortable sensations and reduce pain compared to lower frequencies (2-50 Hz). Stimulus amplitude and pulse duration will be increased until the subject reports that comfortable sensations cover the surgical site (region in which pain is anticipated following surgery). Stimulation parameters will be adjusted to improve stimulation coverage and comfort. The lead will be affixed to the skin with a sterile occlusive dressing (**Figures 4 and 10**). The stimulator will be set to deliver a range of currents which subjects can control themselves. The stimulator will be removed until after surgery.

Figure 10. Inserted electrical lead secured under gauze and a dressing



Subjects will continue to receive usual and customary local anesthetic-based analgesia. Because percutaneous PNS does not induce a sensory block and therefore does not provide anesthesia for the surgical procedure itself, we will continue to provide subjects with preoperative single-injection local anesthetic-based peripheral nerve block(s) (**Table 1**; 20 mL of either ropivacaine 0.5% or bupivacaine 0.5% with epinephrine 1:400,000). In addition, surgeons will be permitted to infiltrate the surgical area with local anesthetic (bupivacaine HCl).

Treatment group assignment (randomization). Subjects will be allocated to a treatment only after confirmation of successfully inserted electrical leads; and will be randomized to one of two possible treatment groups (**Figure 11**):

(1) **Current** delivered via the electrical lead(s) [Experimental group]
(2) **No current** delivered via the electrical lead(s) [Control group]

Figure 11. Treatment groups.

Postoperative Day	0 [day of surgery]	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Experimental	Electric current														
Control	No electric current														

Randomization will be stratified by institution and anatomic lead location (**Table 4**) in a 1:1 ratio and in randomly chosen block sizes. Randomization lists for each enrolling center will be created by the Cleveland Clinic. Treatment group assignment will be conveyed to the enrolling sites via the same secure web-based system (RedCap) used to collect and collate all post-intervention endpoints (see "Data Collection" paragraph below). Stimulators are capable of programming to either (1) pass electrical current; or, (2) not pass electrical current. Importantly, these 2 modes (active and sham) are indistinguishable in appearance, and therefore investigators, subjects, and all clinical staff will be masked to treatment group assignment, with the only exception being the unmasked individual who programs the stimulator (and will not have subsequent contact with the subject). The unmasked personnel will have access to the randomization list on RedCap, program the stimulator appropriately (sham vs. active), and provide the individual subsequently interacting with the study subject with the device without indicating the treatment group.

Subjects will be informed that during postoperative active treatment with electrical current patients do not always have the sensations experienced during preoperative lead placement and once proper placement is confirmed with comfortable sensations, therapeutic levels of stimulation may be delivered sub-threshold (below the intensity required for sensation and still provide relief, which is factual/accurate). ***This protocol will ensure a randomized, double/quadruple-masked, sham/placebo-controlled trial.*** For the feasibility study (UG3), unmasking will occur 2 weeks following surgery to allow for protocol revisions, as necessary ("double masked" during data collection). In contrast, for the definitive pragmatic clinical trial (UH3) unmasking will not occur until statistical analysis and manuscript preparation are complete (termed "quadruple masked").

Intraoperative course. The primary surgical anesthetic will be a general anesthetic, spinal anesthetic or exclusively the preoperative single-injection peripheral nerve block(s). Anesthetics that are also analgesics such as ketamine will not be used: the only permitted analgesic will be intravenous fentanyl, which is anticipated to be minimal since all subjects will receive a single-injection peripheral nerve block immediately prior to surgery.

Postoperative course. Within the recovery room following surgery, the stimulators will be attached to the leads and activated. Operating and recovery room pharmacologic analgesic requirements will be recorded.

Post-hospital course. Prior to discharge, subjects and their caretakers will be provided with verbal and written instructions, the DVPRS scale (pain scale 0-10), and the telephone and pager numbers of a local investigator available at all times during the first two weeks of treatment. Subjects will be discharged home with their leads *in situ*. Subjects will be also be discharged with a prescription for immediate-release oral opioid, preferably oxycodone 5 mg tablets, taken for breakthrough pain. *Therefore, <u>all</u> patients of this study—regardless of the treatment arm they are randomized to—will continue to receive current usual and customary analgesia.* We will attempt to contact subjects the evening of POD 0 to review stimulator instructions, although it is not always possible due to logistical reasons such as a late recovery room discharge. Subjects will be contacted by telephone for end point collection beginning on POD 1. Lead removal will occur on postoperative day 14 (+/- 3 days) by healthcare providers. Similar to perineural catheters,[135] this procedure encompasses simply removing the occlusive dressing and gently pulling on the lead. For resistance during lead withdrawal, lidocaine 1-2% (1-10 mL) may be infiltrated around the lead to relax the peri-lead muscle. Following study completion, the results will be mailed electronically or by the United States Postal Service to all enrolled subjects in written form using non-technical language.

Outcome measurements (end points). We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain-related clinical trials by the World Health Organization and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement.[136] ***Importantly, nearly all outcome measures are common data elements from the National Institute of Neurological Disorders and Stroke (NINDS).***[137] End points (**Table 2**) will be evaluated at baseline (at lead insertion prior to surgery), during the treatment period (postoperative days 1-11); and the follow-up period (postoperative day 18 and months 1, 4, and 12).

Table 2. Summary of post-enrollment assessments (color added for clarity)

Time Point:	Postoperative **Days**	Postoperative **Months**

	0	1	2	3	4	7	11	18	1	4	12
Opioid consumption previous 24 h	•	•	•	•	•	•	•	•	•	•	•
Average Pain [NRS]	•	•	•	•	•	•	•	•	•	•	•
Worst Pain [NRS]	•	•	•	•	•	•	•	•	•	•	•
Brief Pain Inventory, Short Form	•			•		•		•	•	•	•
Defense and Veterans Pain Rating Scale	•	•	•	•	•	•	•	•	•	•	•
World Health Organization **Quality of Life** Instrument	•								•	•	•
Post-Traumatic Stress Disorder Checklist (C)	•										
Masking Assessment		•									

Demographic and medical history. Subjects will have demographic and anthropomorphic data collected based on NINDS case report form General Core and Demographics Modules and Guidelines, including age, sex, height, weight, educational level, employment status, marital status, and U.S. military service (e.g., none, discharged, active). In addition, the medical history based on the common data elements of the NINDS Medical, Family, Behavioral History, History of Disease/Injury Event, and Prior and Concomitant Medications Sub-Domains will be collected, and include the mechanism of original injury, medications (including analgesics), previous surgical procedures, comorbidities, existing sensory deficits of the target nerve distribution, and preoperative pain levels measured on a Numeric Rating Scale for pain (including daily least, average, worst and current). In addition, since post-traumatic stress disorder (PTSD) may be associated with the severity of pain,[138] at baseline we will apply the PTSD Checklist (PCL-C), a 20-item self-report measure reflecting symptoms of PTSD validated in military,[139] Veteran,[140-142] and civilian populations.[143]

Postoperatively, surgical endpoints will be recorded such as surgical duration, tourniquet duration (if applicable), analgesic administration, anesthetic administered, and any sedative agents provided. In addition, subjects will have baseline end points measured including a pain score at the surgical site using the Numeric Rating Scale (NRS, 0-10). ***The remaining end points of Table 2 are described in detail under each Hypothesis in the UH3 Implementation Phase section description below.***

Data collection. Much of the surgical data from the day of surgery will be extracted from electronic health records to leverage data collection that occurs in health care delivery rather than requiring independent research data collection. Subject demographic, surgical and percutaneous PNS administration data will be uploaded from each enrolling center *via* the Internet to a secure,[144] password-protected, encrypted central server (RedCap, Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio).[145] All data collection following the day of enrollment (postoperative day 0)—regardless of enrolling center—will be collected by telephone from the University of California San Diego. Staff masked to treatment group assignment will perform all assessments.

UG3 Milestones. The 2-year UG3 feasibility period has explicit milestones (**Table 3**, following page) that are feasible, quantifiable, and scientifically justified to allow an assessment of progress. ***Each of the items listed in Table 3 and the following outline is considered a milestone and must be completed in order to proceed to the 4-year UH3 definitive, pragmatic clinical trial.***

Study Preparation. Finalize protocol with the Steering Committee, Site Directors, Significant Contributors, and NIH-DoD-VA Pain Management Collaboratory. Finalize common and individual site case report forms (each enrolling site will require forms that conform to its own specific requirements). In concert with the Principal Investigator, the Department of Outcomes Research (Cleveland Clinic, Cleveland, OH) will create the data-entry platform (database) used to store all study-related information. Equipment (e.g., electrical leads and stimulators) will be ordered for each enrolling center. Research Coordinators will be hired and trained at all enrolling centers. The Primary Investigator will visit each of the enrolling centers to train both Site Directors and Research Coordinators in all aspects of the study. In addition, a trained representative from the developer and manufacturer of the percutaneous PNS system (SPR Therapeutics) will travel to each enrolling center to train Site Directors and Research Coordinators on how to insert and manage the leads and stimulators. This will be done at the company's expense, and conform to all HIPAA requirements. Training will continue with successive subjects until both the representative and study personnel feel comfortable with the site's future enrollment without further training.

Table 3. Two-year **UG3** Planning Phase feasibility study **Timeline** (color added for clarity)

Funding Year:	**1**			**2**	
Months (within year):	**1-4**	**5-8**	**9-12**	**1-6**	**6-12**
Identify staff who will participate in NIH-DoD-VA Pain Management Collaboratory Work Groups	•				
Work with NIH-DoD-VA Pain Management Collaboratory to comply with approved policies and practices	•	•	•	•	•
Initiate DSMB and develop DSMB charter	•				
Report to medical monitor (monthly) and DSMB quarterly	•	•	•	•	•
Initiate and complete CRADAs at military treatment facilities	•	•	•		
Finalize preparation for UG3 feasibility study (details below)	•				
Hire/train research coordinators	•				
Prepare training/implementation documents and videos	•				
Prepare data-entry platform at the Cleveland Clinic	•	•			
Enrollment site IRB submissions, reviews and revisions	•	•	•		
NIH-DoD-VA oversight body submission	•	•	•		
Site visits and training by Principal Investigator			•		
Educate clinic contacts (e.g., surgeons) for referrals			•		
Order and prepare equipment			•	•	
Lead/stimulator training for all Site Directors by SPR Therapeutics			•	•	
Register study and update on clinicaltrials.gov				•	•
Subject enrollment (following IRB approval)				•	

Data collection, University California San Diego (Day 1 to Month 4)				•	•
Quality assurance				•	•
Address any ethical, human subject safety and oversight issues				•	•
Assess adequacy of protocol, data-entry platform, and study sites				•	•
Replace any study sites, if necessary					•
Data cleaning and statistical analysis					•
Revise pragmatic clinical trial (UH3) statistical section, as necessary					•
Revise protocol for pragmatic clinical trial (UH3), as necessary					•
If necessary, revise budget for pragmatic clinical trial					•
IRB revisions at enrolling centers and oversight agencies, if needed					•
Manuscript preparation: protocol description					•
Upload results to ClinicalTrials.gov					•
Final UG3 report to funding and oversight agencies					•

CRADA: Cooperative Research and Development Agreement

Regulatory Review and Approval Process. Of note, the entire first year of the funding period is currently designated for this purpose due to the often-prolonged period of time required for regulatory review and approval. However, enrollment may commence sooner if the regulatory process requires less than 1 year. This is probable since the stimulation system used in the proposed investigation is already cleared for use in treating acute pain, and therefore US FDA investigational device exemption approval is not needed and the proposed use in this study is on label. The final protocol will be formatted and then submitted to all enrolling site IRBs and the funding agency's oversight committee (e.g., U.S. Army Medical Research and Materiel Command Human Research Protection Office). The DSMB will be initiated which will design the DSMB charter describing role, reporting procedures, and meeting protocol. A Medical Monitor (DSMB Chair, "subject advocate") and DSMB members will receive quarterly reports prepared by the Principal Investigator (reviews project accomplishments, issues, problems, upcoming goals, adverse events, protocol deviations, etc.). The DSMB will review progress and recommends modification, continuation, or termination:

- Approval of the trial protocol before enrollment
- Review data in order to determine efficacy, futility, and safety, and to determine continuation
- Review data quality and data integrity
- Evaluate risk versus benefit by thorough examination of the data accumulated
- Determine whether the trial is proceeding as planned, the protocol is being followed, the recruitment of patients is on schedule, and data are being collected with the proper accuracy
- Review patient dropouts, if any, and make appropriate recommendations
- Determine whether safety concerns have been raised by the experimental or control treatments
- Modifications of the study protocol based upon the review of the safety data
- Suspension or early termination of the study or of one or more study arms because of serious concerns about patients' safety, inadequate performance, or rate of enrollment

- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines
- Optional approaches for executive committee and investigators to consider when the DSMB determines that the incidence of the primary study outcomes is substantially less than expected, such as recommendations to increase the number of trial centers or extend the recruitment period
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious

Study Implementation. The study will be registered on clinicaltrials.gov prior to enrollment of the first subject, and be kept updated. Research Coordinators will re-educate clinical contacts on ethical referral process and initiate the referral period. For the initial subject at each enrolling center, a trained representative from the developer and manufacturer of the percutaneous PNS system (SPR Therapeutics) will travel to each enrolling center to train both Site Directors and Research Coordinators in how to insert and manage leads and stimulators. For quality assurance, the Principal Investigator will review with the study team the entire first subject's course, from referral to enrollment to lead insertion to medical follow-up and adverse event or protocol deviation reporting.

Enrollment. The Research Coordinator or Site Director at each enrolling center will schedule lead insertions for that specific site. Baseline and day-of-surgery (postoperative day 0) data collection will occur at each enrolling site, with the case report forms faxed to the Principal Investigator at the University California San Diego using a secure fax machine in a locked office to protect personal health information. All data collection following the day of surgery will occur by telephone from the University of California San Diego, which will then enter all data to the database. For the UG3 feasibility study, the final data collection point for each subject will be at 4 months following surgery (the 12-month time point will be used for the definitive UH3 pragmatic clinical trial). Quality assurance will be ongoing by the University of California San Diego, which will monitor data for sources of error and report to the Medical Monitor (DSMB Chair) with written monthly reports. Each enrolling center will be expected to enroll at least 1 subject for each of the 3 possible lead locations (e.g., brachial plexus trunks) in each of the first two quarters of the 2nd year of the funding period. Combined, the 7 centers will enroll a total of 64 subjects as part of the feasibility study.

Preparation for the UH3 Clinical Trial. If one or more centers fails to enroll their designated subjects—for whatever reason(s)—other centers will make up this enrollment with coordination by the Principal Investigator. The 64-subject feasibility study will enable evaluation of the study intervention, protocol, case report forms, outcome measures, data-entry platform, Research Coordinators, Site Directors, and study oversight. Any changes deemed necessary by the Principal Investigator in concert with the DSMB, funding agency, Steering Committee, Site Directors and NIH-DoD-VA Pain Management Collaboratory Coordinating Center will be made to any aspect of the study design (such as the outcome measures or informed consent forms), including replacing any enrolling center that fails to demonstrate the ability to adequately enroll and execute the protocol (following completion of the UG3 phase, the Palo Alto VA and Cleveland Clinic were removed due to a complete lack of enrollment; and Cedars Sinai was added and successfully demonstrated the ability to enroll subjects). The data from the first 64 subjects will be cleaned by University of California San Diego and a statistical analysis performed by the study statistician (Edward Mascha, PhD) at the Department of Outcomes Research (Cleveland Clinic).

In concert with the NIH-DoD-VA Pain Management Collaboratory Coordinating Center, the statistical section for the subsequent UH3 pragmatic clinical trial will be revised to reflect the ***estimated treatment effect*** and treatment group means. For the initial submission, we have estimated the probable maximum sample size for budgeting and planning purposes; but, the results of the initial feasibility study will most-likely decrease the definitive UH3 pragmatic trial required sample size. The statistical section and budget will be revised to reflect any changes. Any revisions to the protocol or informed consent forms will be submitted to the DSMB, individual center IRBs and HRPO. A manuscript with the results of the pilot study will be prepared and submitted with the results concurrently uploaded to ClinicalTrials.gov. Lastly, a final UG3 period report will be prepared for the funding and oversight agencies.

UG3 Planning Phase Specific Aims. The investigation described above will accomplish the two Specific Aims of the UG3 Planning Phase:

Specific Aim 1 (UG3): To determine the **feasibility** and **optimize** the protocol of the Implementation Phase (UH3) multicenter clinical trial that will compare percutaneous PNS with usual and customary opioid-based analgesia following moderate-to-severely painful ambulatory surgery.

Specific Aim 2 (UG3): To ***estimate*** the **treatment effect** of percutaneous PNS on pain and opioid consumption following moderate-to-severely painful ambulatory surgery compared with usual and customary opioid-based analgesia. This will allow determination of the required **sample size** of the definitive multicenter clinical trial of the Implementation Phase (UH3).

UH3 Implementation Phase

The 4-year UH3 Implementation Phase will include a multicenter, randomized, quadruple-masked, placebo-controlled, parallel-arm, human subjects pragmatic clinical trial. The primary Specific Aim of the trial is to determine the effect of percutaneous PNS on postoperative **opioid** requirements and **analgesia** following moderate-to-severely-painful ambulatory surgery (under the usual conditions in which PNS will be applied, making this a “pragmatic trial”). Secondary Specific Aims are to determine the effect of percutaneous PNS on physical and emotional **functioning**, **chronic pain**, and **quality of life** following moderate-to-severely-painful ambulatory surgery. The definitive UH3 pragmatic clinic trial will use the same protocol as the UG3 Planning Phase feasibility study described above, with the addition of any revisions determined necessary following that initial investigation. We will work closely with the NIH-DoD-VA Pain Management Collaboratory Coordinating Center at all phases of the definitive pragmatic clinical trial, from preparation through data analysis and manuscript preparation.

The primary end points will be cumulative opioid consumption and average surgical pain (measured with a Numeric Rating Scale) within the first 7 postoperative days following recovery room discharge. The primary analyses will compare the two treatment groups, one of which will receive active stimulation while the other will receive no stimulation.

Hypothesis 1 (UH3): **Opioid** consumption will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia.

Opioid analgesic consumption will be recorded at all time points (**Table 2**), ***with one co-primary end point being the cumulative opioid dose in oral morphine equivalents for postoperative days 0-7*** (see statistical section for further details).

Hypothesis 2 (UH3): Surgical **pain** will be decreased within the first 7 postoperative days following recovery room discharge with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Current/present, worst, least, and average pain at the surgical site will be assessed using a Numeric Rating Scale (NRS) as part of the Brief Pain Inventory (short form). The Brief Pain Inventory is an approved NINDS common data elements Scale. The use of single items (e.g., average pain) in addition to the composite score is supported by the IMMPACT recommendations for assessing pain in clinical trials. The NRS will be recorded at all time points (**Table 2**), ***with one co-primary end point being the values of the "average" pain scores for the first postoperative week following recovery room discharge, collected on postoperative days 1, 2, 3, 4, and 7*** (see statistical section for further details). The NRS is a highly-sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain. The NRS has been demonstrated to be a valid and reliable measure following analgesic interventions. In addition, NRS scores correlate well with other measures of pain intensity, and demonstrate high test-retest reliability. These NRS characteristics led to recent IMMPACT consensus recommendations for use of the 10-point NRS of pain intensity for pain trials.

An additional instrument, the Defense and Veterans Pain Rating Scale (DVPRS), will be utilized. The DVPRS was developed specifically for—and subsequently validated in—active duty military and Veteran patient populations. Unfortunately, this new instrument has not been validated for repeated measures, and therefore will not be used as a primary end point for the current investigation. However, future pain-related investigations involving military personnel and Veterans will undoubtedly use the DVPRS, and we want the results of the current study to be comparable. Therefore, we will use the DVPRS as a secondary end point.

Primary end point: *In order to claim that percutaneous PNS is superior to usual and customary analgesia, at least one of Hypotheses 1 and 2 above must be superior while the other either superior or at least noninferior.*

Hypothesis 3 (UH3): Physical and emotional **dysfunction** due to pain will be decreased in the 12 months following ambulatory surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the Brief Pain Inventory).

The Brief Pain Inventory (short form) is an instrument specifically designed to assess pain and its impact on physical and emotional functioning. It has established reliability and validity, with minimal inter-rater discordance, is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement, and is an approved NINDS common data elements Scale. The Brief Pain Inventory is comprised of three domains: (1) *pain,* with four questions involving "worst", "average", "least", and "current" pain levels using a 0-10 NRS; (2) percentage of *relief* provided by pain treatments with one question [reported score is the percentage divided by 10 and then subtracted from 10: 0 = complete relief, 10 = no relief]; and, (3) *interference* with 7 questions involving physical and emotional functioning using a 0-10 Likert scale [0 = no interference; 10 = complete interference]: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The 4 questions addressing specific pain levels may be combined into a pain subscale (0-40); and, the 7 interference questions may be combined to produce an interference subscale (0-70), the latter of which will be of primary interest for this study. The use of single items (e.g., average pain), subscales, and the composite score (0 = optimal; 120 = worst possible) is supported by the IMMPACT recommendations for assessing pain in clinical trials. The Brief Pain Inventory has been used in countless clinical studies of chronic pain. This instrument is associated with minimal subject burden and is easily interpreted by patients of all ages and education levels.[160] It has high test-retest reliability and correlates well with much longer questionnaires, including the McGill measures and EuroQol.

***Hypothesis 4 (UH3)**:* The incidence and intensity of **chronic pain** will be decreased 4 and 12 months following surgery with percutaneous PNS compared with usual and customary analgesia (measured with a Numeric Rating Scale).

Current/present, worst, least, and average pain at the surgical site will be assessed using a Numeric Rating Scale (NRS) as part of the Brief Pain Inventory (short form).[151] The use of single items (e.g., average pain) in addition to the composite score is supported by the IMMPACT recommendations for assessing pain in clinical trials and is an approved NINDS common data elements Sub-Scale. Patient "worst" pain will be of primary interest at 4 and 12 months. As described previously, the NRS is a highly-sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain. The NRS has been demonstrated to be a valid and reliable measure following analgesic interventions.

***Hypothesis 5 (UH3)**:* **Quality of life** will be improved 1, 4, and 12 months following surgery with percutaneous PNS as compared with usual and customary analgesia (measured with the World Health Organization Quality of Life-BREF Instrument).

While the primary goal of postoperative analgesics is in providing pain control, the most important outcomes for post-surgical patients are measures of well-being. These measures reflect the dimensions of health as they are conceptualized and valued by patients themselves. While health-related quality of life is a subjective concept, various instruments are available that convert health

status into quantifiable values. The World Health Organization Quality of Life (WHOQoL) Instrument is specifically designed to evaluate clinically important, patient-relevant changes in health-related quality of life. The WHOQoL-BREF was developed by the World Health Organization to focus on those aspects of life most important to patients and is composed of 24 questions assessing 4 dimensions: (1) physical health, (2) psychological health, (3) social relationships, and (4) environment (e.g., participation in and opportunities for recreation). In addition, two items are examined separately and involve individuals' overall perception of both their quality of life and health. Each of the 26 questions is rated on a 0-5 scale, and then summed to produce both a total score as well as domain-specific scores for more in depth analysis. Domain scores are scaled in a positive direction (i.e. higher scores denote higher quality of life). The mean score of items within each domain is used to calculate the domain score. Mean scores are then converted to range between 0-100 to enable comparisons to be made between domains comprised of unequal numbers of questions.

This quality of life instrument has been used in countless clinical investigations of pain, is validated specifically in postoperative populations following orthopedic surgery, and will increase the yield of this trial by improving comparisons with other investigations. This instrument has good clinical acceptability with minimal subject burden and is available in both self- and interviewer-administered formats. It has exceptional internal consistency, intra-rater (test-retest) reliability, construct validity, and discriminant validity.

UH3 Milestones. The 4-year UH3 implementation period has explicit milestones that are feasible, quantifiable, and scientifically justified to allow an assessment of progress. ***Annual milestones are listed below following the timeline (Table 4). All milestones must be completed in order to consider the UH3 definitive, pragmatic clinical trial successfully concluded.***

Table 4. Four-year **UH3** Implementation Phase pragmatic clinical trial **Timeline** (color added for clarity)

Funding Year:	**3**		**4**	**5**		**6**	
Months (within year):	**1-9**	**9-12**		**1-8**	**8-12**	**1-8**	**9-12**
Complete any revisions remaining from UG3 feasibility study	•						
Re-initiate subject enrollment	•						
Continue subject enrollment	•	•	•	•			
Data collection phone calls and database entry	•	•	•	•	•	•	
Medical Monitor reports (every 3 months)	•	•	•	•	•	•	•
DSMB reports (every 3 months)	•	•	•	•	•	•	•
Funding agency / oversight body reports (quarterly)		•	•		•		•
Enrolling center IRB Continuing Reviews		•	•	•	•	•	
Data entry and quality assurance		•	•	•	•	•	
Interim analyses (25%, 50%, 75% enrollment)		•	•	•			
Keep clinicaltrials.gov registry up-to-date		•	•	•	•	•	•
Data cleaning and analysis							•
Final data analysis							•

Results to coinvestigators and interpretation							•
Results sent to all study participants							•
Results sent to funding agency							•
Manuscript preparation and submission							•
Final results uploaded to clinicaltrials.gov							•
Study closure by all regulatory bodies							•
Conclude DSMB with final report							•
Final report to funding agency							•

Any revisions made to the feasibility study protocol and informed consent form (or any other aspect of the project) will have been completed during the last 2 quarters of the previous funding year (and submitted/approved by the appropriate regulatory bodies). Therefore, study staff already well versed in the logistics of the project will implement the protocol. As with the feasibility study, the Principal Investigator will review with the study team the entire first subject's course, from referral to enrollment to lead insertion to medical follow-up and adverse event or protocol deviation reporting for quality assurance. As with the feasibility study, prospective subjects will be identified in surgical clinics, referred to study personnel (adhering to HIPAA guidelines), offered enrollment by Research Coordinators, enrolled with written, informed consent, undergo the intervention and randomization, medical follow-up by the local Site Director, and data collection by the University of California San Diego.

Definitive information about the execution of the intervention will be collected by the Primary Investigator and provided to the funding agency (any deficiencies will be corrected with the Site Directors). As with the feasibility study, monitoring of all Sites will continue by the Primary Investigator, with quarterly reports provided to the Medical Monitor and DSBM, and to the funding agency / oversight body quarterly. The IRB continuing reviews will occur annually at the enrolling centers. Clinicaltrials.gov registry will remain up-to-date. We will continue to work closely with the NIH-DoD-VA Pain Management Collaboratory Coordinating Center regarding all aspects of the project.

Year 3 Milestones [Implementation Phase Year 1]:

- Revise protocol with approval by all regulatory bodies (HRPO and local IRBs)
- Re-initiate enrollment with revised protocol
- Successfully enroll approximately 20% of the total required enrollment
- Successfully collect and upload to the data-collection platform (database) all data from UH3 clinical trial subjects

Year 4 Milestones:

- Successfully enroll approximately 40% of the total required enrollment
- Successfully collect and upload to the data-collection platform (database) all data from UH3 clinical trial subjects
- First and second interim analyses after 25 and 50% of subjects enrolled, respectively
- Continuing approval by all regulatory bodies (DSMB, local IRBs, HRPO)

Year 5 Milestones:

- Successfully enroll the remaining required subjects to complete enrollment
- Successfully collect and upload to the data-collection platform (database) all data from UH3 clinical trial subjects
- Third interim analysis after 75% of subjects enrolled
- Continuing approval by all regulatory bodies (DSMB, local IRBs, HRPO)

Year 6 Milestones:

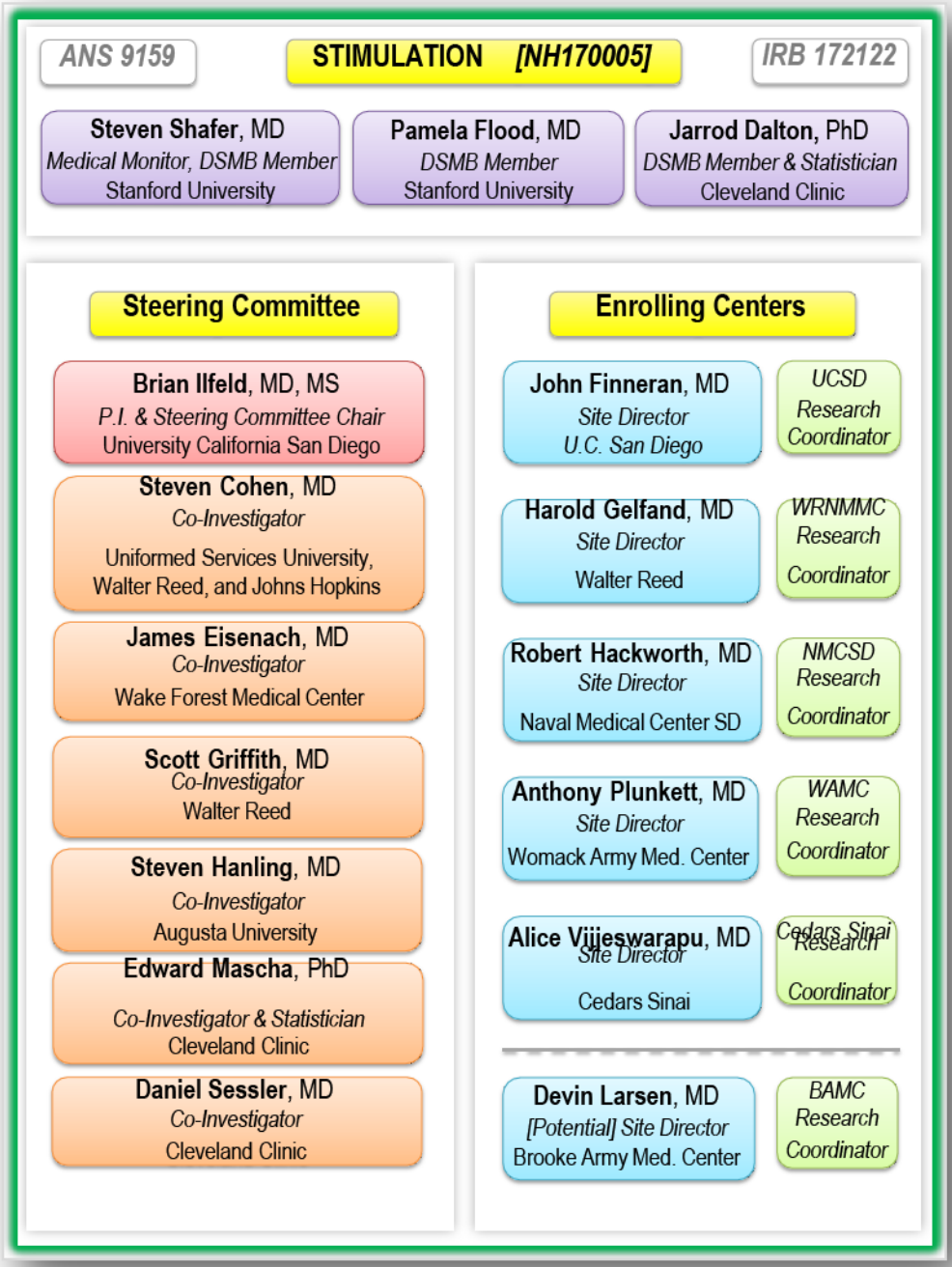
- Complete data collection 1 year following enrollment of the final subject (anticipated 3rd quarter)
- Successfully upload to the data-collection platform (database) final data
- Data cleaning and final analysis
- Results dissemination to coinvestigators and interpretation
- Results sent to funding agency and all study participants (by email or U.S. mail)
- Manuscript preparation and submission
- Clinicaltrials.gov updated with final results
- Study closure by all regulatory bodies (DSMB, local IRBs, HRPO)
- Conclude DSMB with final report
- Final report to funding agency

Medical Monitor. The study will have a designated medical monitor, Steven Shafer, MD, who will remain completely independent of the investigative team and will be a strong subject advocate. The Medical monitor 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.

Figure 12. Institutional projected quarterly enrollment, with the first year dedicated to regulatory approval, the second year for feasibility study enrollment and protocol revisions, 11 quarters of enrollment for the pragmatic clinical trial, a year for subject follow-up, and the final quarter for data analysis and manuscript preparation.

Ending May 15th of…	Year 1 (2019)				Year 2 (2020)				Year 3 (2021)				Year 4 (2022)				Year 5 (2023)				Year 6 (2024)				UG3	UH3	Total
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4			
BAMC									0	-	-	-	-	-	-	-	-	-	-	-					0	**0**	0
Cedars Sinai									1			3	9	9	9	9	9	9	9	9					1	**75**	76
NMCSD									1			1	3	3	3	3	3	3	3	3					1	**25**	26
UCSD			3	6	7	15	9	1	12	1		4	12	12	12	12	12	12	12	12					54	**100**	154
WRNMMC							3	0	0			1	3	3	3	3	3	3	3	3					3	**25**	28
WAMC									2			1	3	3	3	3	3	3	3	3					2	**25**	27
Quarterly Total	0	0	3	6	7	15	12	1	16	1	0	10	30	30	30	30	30	30	30	30	0	0	0	0	61	**250**	311
Yearly Total	9				35				27				120				120				0						

The Study Team (Figure 13). The study team consists of the Principal Investigator, 7 additional members of the Steering Committee, 6 Site Directors, and 1 research coordinator for each of the enrolling centers (Brooke Army Medical Center has regulatory approval to enroll subjects but lost the original Site Director due to an inter-base transfer; BAMC hopes to begin enrollment within the next year with a new Site Director).



Statistical Plan and Data Analysis [UG3 Phase]

Randomized groups will be compared for balance on baseline characteristics using descriptive statistics and the standardized difference (i.e., difference in means or proportions divided by pooled standard deviation). Absolute standardized differences larger than 0.487 (using formula in Austin 2009) will be considered imbalanced and the corresponding variables considered for adjustment in all analyses. Primary analyses will be modified intent-to-treat, such that all randomized patients who receive at least some of the study intervention will be included in the analyses. All patients who

receive at least some of the study intervention will be analyzed and in the group to which they were randomized.

Statistical methods will largely be the same for the Planning Phase (UG3) and the Implementation Phase (UH3). As explained below, one difference is that in the planning phase focus we will be on the estimated confidence interval for the treatment effects and the variability of the outcomes, as these will be used in designing the full trial. Another is that interim analyses and more thorough subgroup analyses will be done in the Implementation Phase. Details are given below.

For Specific Aim 2 we will estimate the treatment effect of PNS versus usual and customary care on pain and opioid consumption using a joint hypothesis testing framework. Specifically, we will conclude PNS is superior to usual and customary analgesia, at least one of Hypotheses 1 and 2 must be superior while the other either superior or at least noninferior.

We will first test for noninferiority of PNS to usual care on each of the two outcomes using 1-tailed noninferiority tests. The noninferiority deltas will be 1 point (worse) in pain score and 20% higher in opioid consumption. Noninferiority will be assessed at the overall 0.05 significance level with no adjustment to the significance criterion for testing two outcomes since noninferiority is required on both outcomes – i.e., an intersection union test. A noninferiority delta of 1 point in pain score is conservative since receiver operating characteristic curve analysis has demonstrated 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.[153,156,177-179]

We will assess noninferiority on pain score using a 1-tailed t-test which incorporates the noninferiority delta of 1 point. The estimated treatment effect for pain score will be derived from a linear mixed effects model with the outcome of patient's "average" pain score for each day (1,2,3,4,7), with fixed effects for intervention (PNS vs usual care), time (days 1 through 7) and assuming an autoregressive correlation structure among the measurements on the same patient over time. We will then test for noninferiority with a 1-tailed t-test in which the numerator is the estimated treatment effect from the model minus the noninferiority delta (1), and the denominator is the standard error of the estimated treatment effect. This method will yield results similar to comparing groups on the patient mean across these seven days but is more flexible since it allows for missing data and also directly accounts for the correlation within patient. The model also allows assessing the treatment-by-time interaction, but this will most likely not be of interest. As a sensitivity analysis we will relax the normality assumption and assess the treatment effect (plus test for noninferiority) on pain score over time using a mixed effects quantile regression model [1] in which we consider patient as a random effect, report the treatment effect as the difference in median pain scores, and use the same noninferiority delta of 1.

Cumulative opioid consumption is not typically normally distributed, but usually approximates a log-normal distribution. We therefore plan to assess the treatment effect of PNS versus usual care on the log transformed cumulative consumption from recovery room discharge through POD 7 using a simple linear regression model (equivalent to a t-test). The estimated treatment effect (i.e., difference between groups) will then be used in a noninferiority test with null and alternative hypotheses as: $H0: \mu1 - \mu2 \geq \log(1.2) = 0.263$ versus $HA: \mu1 - \mu2 < \log(1.2) = 0.263$, where $\mu1$ and $\mu2$ are the means of log-transformed opioid consumption for PNS and usual care, respectively, and $\mu1 - \mu2$ is estimated by the coefficient (i.e., beta) for PNS versus usual care in the regression model. The

estimated treatment effect beta will also be an estimate of the ratio of geometric means for the two groups, assuming data for each group is log-normal with similar coefficient of variation between groups.

In the planning phase, focus will be on the estimated confidence interval for the treatment effects and the variability of the outcomes.

Secondary outcomes will be assessed using appropriate statistical methods. We will use the t-test or Wilcoxon rank sum test for physical and functioning as measured by the Brief Pain Inventory (Hypothesis 3), chi-square analyses and t-test of Wilcoxon rank sum test for incidence and intensity of chronic pain, respectively (Hypothesis 4), and Wilcoxon rank sum for quality of life measure by the World Health Organization Quality of Life-BREF Instrument.

Subgroup analysis for sex. There is little relevant prior experience with the study intervention in the patient population of the proposed investigation, so it is not known whether either sex would interact with the treatment effect. Therefore, in accord with the Human Subjects recommendations, we will assess the treatment effect of PNS on each outcome of interest within sex subgroups. In addition, we will analyze each anatomic location to detect variations in treatment effect among the various lead insertion sites and types of surgical procedures. We will not require a significant interaction between treatment effect and these factors, but will rather conduct the subgroup analyses for each level of sufficient size (n=30). The subgroup analyses will be the same as those conducted on the entire sample, and so would be just as valid and unbiased.

Planning Phase (UG3) sample size considerations. The sample size for the planning phase of 64 patients will be sufficient to estimate the treatment effects of interest with moderate precision, i.e., a confidence interval width of roughly 1.1 standard deviations for each outcome measure. Confidence interval width for a standard deviation estimate will be 0.70 standard deviations. The planning phase will be sufficient to use in estimating the expected treatment effect and standard deviation for each outcome for the larger trial.

Missing outcomes data will be summarized along with a known etiology of the absence. While very little outcomes data is expected to be missing, all analyses will be intention to treat, and imputation of missing data using methods such an multiple imputation and last observation carried forward will therefore be utilized, based on the situation. We may also conduct a conservative analysis in which we assign the worst observed outcome to patients in intervention groups and best observed outcomes to those in control.

Throughout, the significance level will be 0.05 for each hypothesis. SAS statistical software (Cary, NC) will be used for all analyses, and East 6.0 (Cytel, Inc. Cambridge, MA) for interim monitoring and sample size calculations.

Statistical Plan and Data Analysis: Implementation Phase [UH3]

Randomized groups will be compared for balance on baseline characteristics using descriptive statistics and the standardized difference (i.e., difference in means or proportions divided by pooled standard deviation). Absolute standardized differences larger than 0.10 will be considered imbalanced and the corresponding variables considered for adjustment in all analyses.[2] Primary

analyses will be modified intent-to-treat, such that all randomized patients who receive at least some of the study intervention will be included in the analyses. All patients will be analyzed in the group to which they were randomized. Statistical methods for the Implementation Phase will generally follow the analyses conducted in the Pilot (UG3) phase.

Primary Aim. For Specific Aim 1 we will estimate the treatment effect of PNS versus usual and customary care on pain and opioid consumption using a joint hypothesis testing framework.[3] Specifically, we will conclude PNS is more effective than usual and customary analgesia if it is found to be superior on at least one of pain score or opioid consumption and not worse, i.e., noninferior, on both.

Noninferiority Testing. We will first test for noninferiority of PNS to usual care on each of the two outcomes using 1-tailed tests. The noninferiority deltas will be 1 point (worse) in pain score and 20% higher in opioid consumption. Noninferiority will be assessed at the overall (1-tailed) 0.025 significance level with no adjustment to the significance criterion for testing two outcomes since noninferiority is required on both outcomes – i.e., an intersection-union test. A noninferiority delta of 1 point in pain score is appropriate for between-group comparisons because it is about half the difference that would be considered clinically relevant for intra-subject changes: receiver operating characteristic curve analysis has demonstrated 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.[153,156,177-179]

We will assess noninferiority on pain score using a 1-tailed t-test which incorporates the noninferiority delta of 1 point. The estimated treatment effect for pain score will be derived from a linear mixed effects model with the outcome of patient's "average" pain score for each day (1,2,3,4,7), with fixed effects for intervention (PNS vs usual care), time (days 1 through 7) and baseline average pain score, and assuming an autoregressive (AR(1)) correlation structure among the measurements on the same patient over time. We will then test for noninferiority with a 1-tailed t-test in which the numerator is the estimated treatment effect from the model minus the noninferiority delta (1), and the denominator is the standard error of the estimated treatment effect.[4] This method will yield results similar to comparing groups on the patient mean across these seven days but is more flexible since it allows for missing data and also directly accounts for the correlation within patient. The model further allows assessing the treatment-by-time interaction, but this will be only of secondary clinical interest. As a sensitivity analysis we will relax the normality assumption and assess the treatment effect (plus test for noninferiority) on pain score over time using a mixed effects quantile regression model [1] in which we consider patient as a random effect, report the treatment effect as the difference in median pain scores, and use the same noninferiority delta of 1.

Cumulative opioid consumption is not typically normally distributed, and usually approximates a log-normal distribution, as in the pilot trial. We therefore plan to assess the treatment effect of PNS versus usual care on the log-transformed cumulative consumption through POD 7 using a linear regression model in which we adjust for any imbalanced baseline variables. The estimated treatment effect (i.e., difference between groups) will then be used in a noninferiority test with null and alternative hypotheses as: H0: $\mu 1 - \mu 2 \geq \log(1.2) = 0.263$ versus HA: $\mu 1 - \mu 2 < \log(1.2) = 0.263$, where $\mu 1$ and $\mu 2$ are the means of log-transformed opioid consumption for PNS and usual care, respectively, and $\mu 1 - \mu 2$ is estimated by the coefficient (i.e., beta) for PNS versus usual care in the regression model. The estimated treatment effect in the model will also be an estimate of the

ratio of geometric means for the two groups, assuming data for each group is log-normal with similar coefficient of variation between groups.

Superiority Testing. If noninferiority is found on both pain and opioid consumption we will test for superiority on each outcome using 1-tailed tests in the same direction. For superiority testing, since superiority on either outcome would be sufficient to reject the joint null hypothesis (i.e., a union-intersection test), we will control the type I error at 0.025 across the 2 outcomes by using a Bonferroni correction and using 0.025/2=0.0125 as the significance criterion.

Secondary Outcomes. We will assess the treatment effect on secondary outcomes using appropriate statistical methods. We will use a linear mixed effects model to assess the treatment effect over time for additional outcomes measured at days POD 1-7 (1, 2, 3, 4, 7), as in the primary analysis, including worst pain and the Defense and Veterans Pain Rating Scale; similarly we will assess the treatment effect on total severity score and total interference score at days 3 and 7. As sensitivity analyses we will also use a generalized ordinal regression model for each of these outcomes. For outcomes analyzed at a single time point (days 11, 18; months 1, 4, 12) we will use 2-sample t-test or Wilcoxon rank sum test for physical and functioning as measured by the Brief Pain Inventory (Hypothesis 3), chi-square analyses and t-test of Wilcoxon rank sum test for incidence and intensity of chronic pain, respectively (Hypothesis 4), and Wilcoxon rank sum test for quality of life measure by the World Health Organization Quality of Life-BREF Instrument. Analogous regression models would be used, as needed, to adjust for baseline imbalance.

Study-wide Type I error control. We will use a parallel gatekeeping procedure [1,5,6] to control the study-wide type I error at 0.05. For this procedure we *a priori* prioritize the study outcomes into 10 ordered sets, as given in **Table 5**. 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 0.025 [for each direction of interest; primary outcomes being 1-sided and all others 2-sided] 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 or Holm-Bonferroni correction) will be used as appropriate to control the type I error at the appropriate level.

Table 5. Ordered sets for Parallel Gatekeeping Procedure

Ordered Set #	Outcome(s)	Measurement Timing ^
1	Primary outcomes Average pain, opioid consumption	POD 1-7
2	Worst pain score	POD 1-7
	DVPRS	POD 1-7
3	BPI interference subscale	POD3, POD7
4	Worst pain	POD 1-11
	DVPRS	"
	Average pain	"
5	Worst pain	Months 4, and 12
6	Worst pain	POD 18
	DVPRS	"
	Average pain	"

7	Worst pain	Month 1
	DVPRS	"
	Average pain	"
8	Worst pain	Month 4
	DVPRS	"
	Average pain	"
9	BPI interference subscale	Months 1, 4, and 12
	WHO-DAS	"

* Additional outcome measures and time points, such as least and current pain levels (from the BPI) will be considered exploratory and not compared statistically

^ throughout, POD 1 refers to POD 0 after PACU through POD1

Assessment of treatment effect heterogeneity. There is little relevant prior experience with the study intervention in the patient population of the proposed investigation, so it is not known whether either sex would interact with the treatment effect. Therefore, in accord with the Human Subjects recommendations, we will assess the treatment effect of PNS on the primary outcomes of interest (pain score, opioid consumption) within levels of sex, and asses the interaction. In addition, we will assess treatment effect heterogeneity across within anatomical locations across the various lead insertion sites, across types of surgical procedures, and across levels of other baseline characteristics as listed below. We will assess the treatment-by-covariate interaction in the appropriate statistical model (i.e., the model used in the primary analyses). We will report the treatment effect within levels of each factor whether or not a significant interaction ($P<0.10$) is found.

We will assess treatment effect heterogeneity across levels of the following variables:

- sex (male, female)
- military (BAMC, WAMC, WRNMMC and NMCSD) vs. civilian (Cedars and UCSD)
- baseline average NRS (< 4, ≥ 4)
- baseline DVPRS (< 5, ≥ 5)
- baseline interference scale of the BPI < 20, ≥ 20)
- duration of surgery (< 90 min, ≥ 90 min)
- bupivacaine vs. ropivacaine (for the initial peripheral nerve block)
- saphenous nerve block (versus not) for lower extremity surgeries
- surgical site (shoulder, foot, ankle)
- surgical procedure (rotator cuff repair, hallux valgus, ankle arthrodesis, ankle arthroplasty)
- for brachial plexus leads: lead positioning (posterior to roots, superior trunk, middle trunk, other)
- for sciatic leads: lead positioning (medial, lateral)
- for sciatic leads: lead positioning (anterior, posterior)

Missing Data. While based on our UG3 results very little missing outcome data is expected, any missing data will be summarized overall and by randomized group along with the known/presumed etiology of the absence. If the missing data for an analysis appear to be missing at random for an outcome which is only designed to be measured once for a patient, we will assign values using multiple imputation (using 5 imputed datasets, and aggregating results across them) in which all other available baseline and outcome data will be used to predict the missing data point(s).[7] For longitudinal outcomes such as the primary outcome pain score, if data appear largely to be missing at random and with comparable frequency between groups, and all patients have at least some non-

missing data, we will ignore the missing data for the primary analysis. If there would be a non-trivial amount of missing data (e.g., > 10 percent missing) for a particular outcome, and the data did not appear in general to be missing at random, we would consider implementing a pattern mixture model approach in which randomized groups are compared on outcome within subgroups defined by the pattern of missing data, for e.g., with results then aggregated across patterns.

Interim Analyses for Efficacy and Futility. A substantive difference from the planning phase is that in the full trial we will conduct interim analyses to assess efficacy and futility at each 25% of the maximum planned enrollment. We will use a group sequential design with gamma spending function[8] and gamma parameters of -4 (quite conservative) for efficacy and -2 (moderately conservative) for futility (**Figure 14**). Assuming the alternative hypotheses were true, the probability of crossing a boundary for either efficacy (mainly) or futility at the first through fourth looks would be 0.07, 0.36, 0.75 and 1.0, respectively.

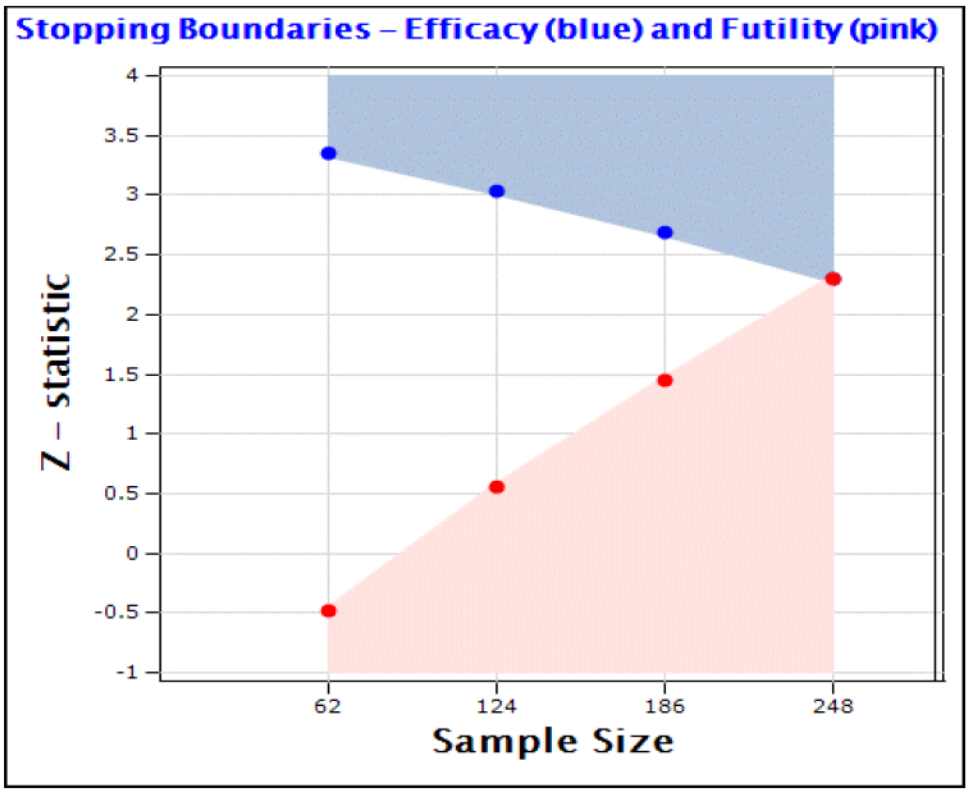


Figure 14. Stopping boundaries for 1-tailed tests for superiority for either pain score or opioid consumption. Blue region indicates superiority (reduced opioid consumption or pain score) and pink region indicates futility (lack of superiority). Z-statistic represents strength of evidence against the null hypothesis, either ratio of means or difference in means, each divided by standard error.

Sample size Justification and Considerations [UH3 Implementation Phase]. Sample size parameters for the implementation phase were informed from our estimates in the planning phase which included N=31 Stimulation and N=34 Placebo patients. For this full trial we choose a sample size which will maintain an overall 90% power at the 0.025 significance level (since 1-tailed tests) to claim the intervention more effective than the control on postoperative opioid requirements and pain

as measured by NRS pain score in our joint hypothesis testing framework. We plan the study to have 90% power to detect superiority on either outcome and at least noninferiority on both. Power for the joint hypothesis testing will be driven by superiority tests since superiority is needed for at least 1 of the 2 outcomes.

Opioid consumption. For cumulative opioid consumption through POD 7 our pilot study data had a coefficient of variation (CV) of 136% (mean (SD) of 17.9 ± 24.3 mg) for the Stimulation patients, 109% (mean (SD) of 17.9 ± 24.3 mg) for Placebo patients, and 142% (mean (SD) of 48 ± 68) overall. The ratio of geometric means (97.5% CI) in the pilot study was 0.20 (0.07, 0.57), for an 80% observed relative reduction, with confidence interval including as small as a 43% reduction.

For the implementation phase we conservatively assume a coefficient of variation of 150% for each group in opioid consumption through 7 days and plan for at least a 40% relative reduction. With these assumptions we will need a total of N= 228 patients to have 90% power to detect a relative reduction of 40% or more (i.e., ratio of geometric means of 0.60 or stronger) in mean opioid consumption at the overall 0.025 1-tailed significance level (0.0125 for each of the two 1-tailed tests for superiority). We use 1-tailed tests here because in the analysis we will only test for superiority after noninferiority of stimulation to placebo has been found. **After adjusting for interim analyses the required maximum total sample size is 250 (125 per group).**

With a sample size of 250 total we would further have 90% power to detect noninferiority in opioid consumption using a noninferiority delta of 1.2 for the ratio of geometric means after assuming a coefficient of variation of 150% and a true ratio of means of 0.75 or more. For a scenario with equal means (ratio of 1.0) we would only have about 25% power to detect noninferiority.

Pain score. In our pilot study we observed a reduction in the mean (97.5%CI) of average pain score of -1.7 (-2.5, -0.85) in Stimulation versus Placebo in the linear mixed effects model across POD1-7. We also observed a within-group standard deviation of pain score ranging from 1.1 to 2.6 across POD 1-7, and values of 1.1 for Stimulation and 1.7 for Placebo for the patient mean across those days. Finally, we observed an intraclass correlation of 0.47 for pain score in the linear mixed effects model across POD1-7. We used these estimates below in assessing the power and sample size for average pain score the implementation phase.

A difference between groups of 1.0 in average pain score is the smallest that would be considered clinically important. With a maximum total sample size of **250** we will have 95% power at the overall 0.025 1-tailed significance level (0.0125 for each of the two 1-tailed tests for superiority) to detect a difference of 1.0 or more between Stimulation and Placebo on mean pain score conservatively assuming a SD of 2.5 for pain score at each day (1, 2, 3, 4, 7) and ICC of 0.50.

Power for Subgroup Analyses. A main difference from the Planning/Pilot phase is that in this full trial we will have sufficient data to conduct the subgroup analyses and we also will have power to detect smaller treatment effects. For example, with 250 total patients, we would have about 90% power to detect a ratio of geometric means of 0.50 or stronger (smaller than observed in the pilot study) in subgroups of size N=125.

The overall significance level will be 0.025 for the primary aim when assessing noninferiority and superiority in 1-tailed tests, and 0.05 when assessing for superiority on secondary outcomes in both

directions. SAS statistical software (Cary, NC) will be used for all analyses, and East 6.0 (Cytel, Inc. Cambridge, MA) for interim monitoring and sample size calculations.

10. HUMAN SUBJECTS

Inclusion criteria: (1) Adult patients of at least 18 years of age; (2) with a planned single-injection peripheral nerve block(s); and (3) undergoing one of the following as a primary surgical procedure:

a. rotator cuff repair (shoulder)
b. ankle arthrodesis
c. ankle arthroplasty
d. hallux valgus correction ("bunionectomy" of the foot)

Exclusion criteria: (1) chronic opioid or tramadol use (daily use within the 2 weeks prior to surgery and duration of use > 4 weeks); (2) neuro-muscular deficit of the surgical limb; (3) compromised immune system based on medical history (e.g., immunosuppressive therapies such as chemotherapy, radiation, sepsis, infection), or other conditions that places the subject at increased risk; (4) implanted spinal cord stimulator, cardiac pacemaker/defibrillator, deep brain stimulator, or other implantable neurostimulator whose stimulus current pathway may overlap; (5) history of bleeding disorder; (6) antiplatelet or anticoagulation therapies other than aspirin due to the risk of bleeding with a 20-gauge insertion needle; (7) allergy to skin-contact materials (occlusive dressings, bandages, tape etc.); (8) incarceration; (9) pregnancy; (10) chronic pain of greater than 3 months in an anatomic location other than the surgical site; (11) anxiety disorder; (12) history of substance abuse; or (13) inability to contact the investigators during the treatment period, and vice versa (e.g., lack of telephone access).

For the initial pilot (UG3) study, to date 57 and 67 subjects have been enrolled at UC San Diego all centers combined, respectively (it is ongoing until we begin the UH3 definitive trial). For the definitive (UH3) study, anticipated enrollment at UCSD will be 125 subjects and anticipated enrollment at all other centers will be 125 subjects. Allowing for 83 additional subjects to account for drop-outs, the project at all enrolling centers for both UG3 and UH3 studies will enroll up to 400 subjects.

11. RECRUITMENT AND PROCEDURES PREPARATORY TO RESEARCH

Enrollment. Surgeons, anesthesiologists or their counterparts (e.g., CRNAs, PAs) at each enrolling center will identify potential study subjects at preoperative patient visits prior to surgery. Surgeons will be seeing patients as part of regular medical care, and therefore this protocol will adhere to Health Insurance Portability and Accountability Act (HIPAA) regulations. Alternatively, the investigators may need to contact potential subjects prior to their pre-surgery visit and therefore request a waiver of consent for recruitment purposes. We will scan the upcoming ambulatory surgery schedule (which we have access to being anesthesiologists—we use this schedule daily for medical purposes), identify patients having the types of surgical procedures specified for this study, look in their electronic records to determine eligibility, and if eligible either call the potential subjects ourselves or provide the name and contact information to a research coordinator to contact the potential subjects.

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

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

3. This clinical trial could not be practicably carried out without the waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or, they are seen just 1-2 days prior to their date of surgery. We need to bring subjects into clinic within the 7 days prior to their surgery to have their leads inserted. We do not have enough time to do this the morning of surgery.

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

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

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

2. This clinical trial could not be practicably carried out without the waiver because many relatively healthy ambulatory patients are not seen in preop clinic; or, they are seen just 1-2 days prior to their date of surgery. We need to bring subjects into clinic within the 7 days prior to their surgery to have their leads inserted. We do not have enough time to do this the morning of surgery.

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

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

Patients meeting inclusion and exclusion criteria will be presented with the study, and prospective study subjects desiring additional information will be required to give permission for a research coordinator to contact them to adhere to HIPAA requirements. The study protocol will be reviewed with interested prospective subjects in detail; and, for subjects desiring participation, written, informed consent will be obtained prior to any measurements, data collection, and/or interventions. The

method of documenting consent will be using written informed consent forms approved by the local Institutional Review Board.

12. INFORMED CONSENT

Once a prospective subject contacts (or gives permission to be contacted by) an investigator or research coordinator by telephone or email, they will be provided information on the study purpose and protocol, as well as have any questions answered. Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled to arrive the day of surgery earlier than normal to allow for written informed consent and baseline instruments to be applied. Written informed consent will be attained prior to any measurements or procedures prior to surgery. Each site director is responsible for ensuring that written, informed consent is obtained from every subject at their respective enrolling center. Clinical research coordinators—also one for each enrolling site—will be specifically trained by the site directors to provide informed consent followed by documentation of informed consent using an Institutional Review Board-approved informed consent form. When subjects present for surgery, research coordinators will provide and attain written informed consent. This will occur in private patient care areas, so that subjects may feel comfortable asking questions of the research coordinator. If a subject desires—or if there is a question that a research coordinator cannot answer—the site director will be called in by the research coordinator to discuss the study directly with the subject.

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

This study protocol has follow-up data-collection telephone calls a maximum of 1 year following the initial study treatment, so repeated informed consent following the initial consent is unnecessary, as opposed to multi-year, longer-term clinical trials. Surrogate consent will not be accepted; therefore, if human subjects cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative is unacceptable for study enrollment.

13. ALTERNATIVES TO STUDY PARTICIPATION

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

14. POTENTIAL RISKS

The procedures and devices used in this study are already 510k cleared by the United States Food and Drug Administration to provide postoperative analgesia. However, there may be risks that are not yet known, and the incidences provided are all estimated with the exception of lead fracture. Potential risks include infection (<0.01% for up to 60 days of infusion),[5] lead fracture (7.5%), lead

dislodgement (<1%), nerve injury (<0.001%), bleeding (<0.01%), skin irritation (1-5%), lead migration (<0.1%), increased surgical pain, and discomfort/pain on insertion and/or during stimulation (10%).

If the patient's surgeon permits a continuous peripheral nerve block (a perineural local anesthetic infusion for 1-2 days following the resolution of their single-injection peripheral nerve block), the participants in this study might have increased pain during this 1-2 day time period should they be randomized to sham or randomized to the active treatment which does not proof effective. Not all surgeons at UC San Diego use continuous peripheral nerve blocks; and those who do use them do so for some patients, but not others (depending on various surgical factors or simply their opinion of the technique). Of note, no other enrolling center offers continuous peripheral nerve blocks to its patients, so this particular risk to study participants is applicable only at UC San Diego (and therefore is included in the informed consent form exclusively for this enrolling center).

In addition, there is the risk of loss of confidentiality. The following study procedures will be done to maintain confidentiality of this study: hard copies will be kept in locked medical offices and the locked Investigational Drug Service's files. Any digitized records containing personal health information will be stored as password-protected and encrypted files.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

The principal protection for participants and the true foundation for conducting a safe and effective clinical study is a well-trained and caring research staff. The principal investigator of this proposal, Dr. Brian Ilfeld, is an experienced multicenter clinical trial Principal Investigator with a Master of Science Degree in Clinical Investigation that included multiple classes specifically addressing the ethical conduct of human subjects research. Dr. Ilfeld has published special articles within peer-reviewed journals specifically addressing this issue (Ilfeld BM: Informed consent for medical research: an ethical imperative. *Reg Anesth Pain Med* 2006; 31: 353-7. PMID: 16857555). All study personnel will receive training in human subjects protection and compliance with the HIPAA regulations.

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). During stimulation, subjects will be contacted a minimum of once every 4 days by an investigator, 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 lead removal. This procedure has proven effective for ambulatory surgical patients with percutaneous peripheral nerve stimulation during the UG3 pilot study.

Precautions and responses to possible specific adverse events:

Infection: Leads will be placed under sterile conditions as is standard-of-care for any percutaneous device insertion. In addition, all patients having orthopedic surgical procedures receive perioperative antibiotics, which will further decrease any risk of infection. Subjects will be called daily and asked about signs and symptoms of lead infection. Should a lead become infected, it will be removed and oral antibiotics prescribed.

Lead fracture: It remains unknown what leads to lead fracture in a small percentage of patients, and therefore we cannot take specific steps to minimize its occurrence other than removing the leads with continuous, gentle traction.

Lead dislodgement and migration: Leads include a small "anchor" at the distal end to help keep the lead from withdrawing. In addition, the leads are shaped as a helical coil, which means they "unravel" if pulled on outside of the skin—the tip of the lead is withdrawn only after the entire lead has uncoiled with traction. Therefore, inadvertent dislodgement and migration are extremely unlikely. An occlusive dressing is used to affix the lead to the skin.

Nerve injury: Leads never intentionally come into contact with the nerve—they are inserted 0.5-2.0 cm distant from the target nerve. Therefore, a nerve injury should—theoretically—only occur with accidental contact with the target nerve. The investigators are all specifically trained and have experience inserting perineural catheters using ultrasound guidance, which permits real-time visualization of the insertion needle and target nerve.

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

Discomfort: Subjects will have a single-injection peripheral nerve block with long-acting local anesthetic prior to surgery and be provided with a prescription for an oral opioid. Therefore, if the electrical leads provide an inadequate degree of analgesia, subjects will take their oral opioids.

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

The study will have a designated medical monitor, Steven Shafer, MD, who will remain completely independent of the investigative team and will be a strong subject advocate. The Medical monitor 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.

The study Data Safety Monitoring Board (DSMB) will be comprised of the Medical Monitor, a physician experienced in both clinical trial management and the ethical conduct of research (Pamela Flood, MD), and a statistician, also well-experienced in multicenter trials (Jarrod Dalton, PhD). All three of these individuals will be completely independent of the investigative team. No member of the DSMB will have any financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. The board will comprise individuals with no vested interest in the outcome of the research study. The members will also sign a confidentiality

statement. The DSMB will operate from a charter describing its role, membership, reporting procedures, and meeting protocol. The DSMB will decide on its own protocols, set triggers for data review or analyses, and establish guidelines for monitoring the study, stopping the study for safety concerns, and for efficacy based on plans specified in the protocol. Confidentiality will be maintained during all phases of DSMB review and deliberations. DSMB members will maintain strict confidentiality concerning all privileged trial results provided to them. The board will perform the following functions:

- Approval of the trial protocol before enrollment of patients
- Review the data in order to determine efficacy, futility, and safety, and to determine whether the study should continue
- Review data quality and data integrity
- Evaluate risk versus benefit by thorough examination of the data accumulated
- Determine whether the trial is proceeding as planned, the protocol is being followed, the recruitment of patients is on schedule, and data are being collected with the proper accuracy
- Review patient dropouts, if any, and make appropriate recommendations
- Determine whether safety concerns have been raised by the experimental or control treatments

Review Items. Items to be reviewed by the DSMB include:
- Interim/cumulative data for evidence of study-related adverse events
- Interim/cumulative data for evidence of efficacy according to pre-established statistical guidelines in the study protocol
- Data quality, completeness, and timeliness
- Performance of individual centers
- Adequacy of compliance with goals for recruitment and retention, including those related to participation of women and minorities
- Adherence to the protocol
- Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations etc.)
- Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study

Recommendations. The DSMB will conclude each review with their recommendations to the principal investigator and primary site Institutional Review Board (at the University of California San Diego) as to whether the study should continue without change, be modified, or terminated. Recommendations regarding modification of the design and conduct of the study may include:
- Modifications of the study protocol based upon the review of the safety data
- Suspension or early termination of the study or of one or more study arms because of serious concerns about patients' safety, inadequate performance, or rate of enrollment
- Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines
- Optional approaches for executive committee and investigators to consider when the DSMB determines that the incidence of the primary study outcomes is substantially less than expected, such as recommendations to increase the number of trial centers or extend the recruitment period
- Corrective actions regarding a study center whose performance appears unsatisfactory or suspicious

Appropriate reports will be made to the Institutional Review Boards at all enrolling centers and the executive committee, comprised of all co-investigators and site directors

Patient Serious Adverse Event Reporting. All unanticipated events and adverse events will be reported to the specific center's Institutional Review Board (IRB), the primary supervising IRB (University of California San Diego), the study Data and Safety Monitoring Board (DSMB), and the Army Human Research Protections Office. The adverse event and unanticipated event profile will be discussed at monthly executive committee video-conference meetings.

Management of adverse events. Adverse events for study-related injuries will be managed by the site director of each center. For a medical emergency that is potentially life-threatening, subjects will be instructed to dial 911 for emergency services to go directly to their location, and the site director will meet the subject at the site's emergency department.

In the event of a study-related injury, the treatment institutions will provide medical care needed to treat those injuries without cost to study subjects. The institutions will not provide any other form of compensation for study-related injuries. This information is specified within the informed consent forms. The forms also instruct subjects to contact the local Institutional Review Board, the enrolling investigator, or the principal investigator of the study for further information (phone numbers provided for all entities). In addition, active duty United States Armed Forces service members who enrolled at a civilian institution who sustain a research-related injury may receive medical care at a military hospital or clinic free of charge. The informed consent form instructs active duty service members to contact the United States Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) for issues that are inadequately resolved (with phone number).

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Pre-ICF information. The only information that will be recorded on hard-copy format before a subject provides written, informed consent is date of surgery, surgeon, name, contact phone numbers, and email address. This information will be destroyed using a paper shredder (or in the locked UCSD PHI disposal stations) following contact with the patient. If the patient does not participate, then there will be no record of PHI whatsoever.

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.

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

Subjects might experience less postoperative pain than they otherwise would have without participation. If so, they might require fewer opioid analgesics and have a lower risk of experiencing opioid-related side effects such as nausea, vomiting, and pruritus. They might have a lower risk of chronic pain, opioid dependence, and mental/physical disability. Lastly, if the participant's surgeon permits continuous nerve blocks and they participate in this study, the participant will not be exposed to the risks of this technique which includes infection (1%), catheter dislodgement (5-10%), and local anesthetic toxicity (very rare).

18. RISK/BENEFIT RATIO

While there are risks involved in the insertion, use, and removal of percutaneous leads, they are relatively rare and not catastrophic when they do occur. With its ease of insertion, prolonged duration of action, presumably lower risk of complications or side effects, and simple removal, neuromodulation has the very real possibility of replacing local anesthetic administration—the standard of care for the past 100 years—that would completely revolutionize postoperative analgesia, as we know it.

19. EXPENSE TO PARTICIPANT

There will be no additional costs to subjects as a result of being in this study, other than any transportation costs and parking charges for their return trip for lead removal. If a subject is injured as a direct result of participation in this research, the University of California will provide any medical care they need to treat those injuries. The University will not provide any other form of compensation for an injury.

20. COMPENSATION FOR PARTICIPATION

There is no compensation for participation.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator, **Brian M. Ilfeld, MD, MS,** is a board-certified anesthesiologist with fellowship training in and 19 post-training years experience with regional anesthesia and acute pain medicine. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC

Medical Centers. Dr. Ilfeld, or another investigator, will follow all subjects following their treatment. Dr. Ilfeld will be responsible for the overall management of this study, as well as for the well-being of study subjects.

Co-investigators, **John Finneran, MD**; **Engy Said, MD; Rodney Gabriel, MD, MAS; and Matthew Swisher, MD;** are board-certified anesthesiologists with fellowship training in and extensive experience with regional anesthesia and acute pain medicine. All hold a license to practice medicine in California and have medical privileges at the UC Medical Centers. All will help consent subjects, perform a history and physical exam, perform the treatment on subjects, and will follow subjects following their treatment.

The study will be overseen a medical monitor, **Steven Shafer, MD**, of Stanford University, Stanford, California—in essence a study subject advocate. As the former Editor-in-Chief of one of anesthesiology's two highest-impact medical journals, a clinician, and a Federally-funded research himself, Dr. Shafer is thoroughly experienced in management of clinical trials, the ethical conduct of clinical research, the patient population under investigation, and Acute Pain Medicine interventions for postoperative analgesia. As such, Dr. Shafer is a strong study subject advocate. Dr. Shafer has extensive experience working on committees and authoring/editing peer-reviewed evidence-based publications, and will be an active member of the DSMB. He has been, and will continue to be, completely independent of the investigative team. In addition, Dr. Shafer has no financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the DSMB. Lastly, he has no vested interest in the outcome of the research study. Dr. Shafer will remain completely independent of the investigative team and will be a strong subject advocate. The Medical monitor 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.

DSMB members Pamela Flood, MD, and Jarrod Dalton, PhD, are from Stanford University and the Cleveland Clinic, respectively. Dr. Flood is a board-certified anesthesiologist and clinical researcher in the with extensive experience involving the ethics of human subjects research. Dr. Dalton is a statistician with 15 years of experience involving clinical research.

Baharin Abdullah is a project manager with the UCSD Department of Anesthesiology; and **Jeffrey Mills** is a research coordinator with the UCSD CTRI. Both individuals have the required training—including up-to-date CITI training—for their positions.

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23. FUNDING SUPPORT FOR THIS STUDY

Drs. Ilfeld and Finneran will be supported by a Department of Defense grant award (NH170005) which will help to support his nonclinical time and the product used in this investigation. Start date for this grant was May 15, 2018 and will terminate after 6 years. Please contact Yolanda Boyd, grants specialist, at (619) 471-3320 for information regarding this DoD grant. All funding for this investigation is provided by the Department of Defense.

24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT
Not applicable.
25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER
Not applicable.
26. IMPACT ON STAFF
None. All study procedures will be executed by investigators and research coordinators without the assistance of non-investigator staff members.
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
None.
30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT
Not applicable: surrogate consent will not be accepted.

Protocol Summary of Changes

Dated May 2021, following enrollment of the first participant

UCSD Human Research Protections Program
COVER LETTER FOR REQUEST
CHANGE/MODIFICATION TO AN APPROVED STUDY

All modifications/changes in a project must be received and approved by the Institutional Review Board *before* they are initiated except where necessary to eliminate apparent immediate hazard to the subject.

If the request for change/modification is only for a personnel change use the Personnel Changes Only cover letter

Identifying Information				
Project	Number:	172122	Principal Investigator:	Brian M. Ilfeld, MD, MS
	Title:	Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation: A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain		
Submitter	Name:	Brian M. Ilfeld, MD, MS		
	E-mail:	bilfeld@ucsd.edu		

1. Why are change(s)/modification(s) being requested?

Clearly and specifically describe the rationale for each of the changes as determined by the PI.

The Principal Investigator consents all subjects without exception, and when he began the study years ago, surgeons were not using continuous peripheral nerve blocks for the patients offered enrollment. However, as time has passed, more and more surgeons are using them for more and more patient indications. As this transition has occurred, the Principal Investigator has explained these potential risks and benefits verbally to any patient who had planned to use a continuous peripheral nerve block. Most patients who were in this situation chose study participation because they would get a single-injection peripheral nerve block that lasts 12-20 hours anyways, and so they preferred to trade definite local anesthetic infusion for 1-2 days past the resolution of their single-injection nerve block for the possibility of 14 days of peripheral nerve stimulation. In reviewing an ICF recently, I believe that this risk should be more explicit than currently included (the ICF notes that increased pain is a possible risk of study participation, but it does not detail exactly why this is the case or how long the possible increased pain might occur). Therefore, I am rectifying the situation now that I have identified it. I want to change the informed consent form and research plan to reflect the fact that if some patients choose to enroll in the study and their surgeons (and anesthesiologists) allow for a continuous peripheral nerve block, the participant will need to forego the continuous peripheral nerve block with possible risks and benefits associated with that decision (although they will still receive a single-injection peripheral nerve block).

2. What change(s)/modification(s) are being requested?

Clearly and specifically describe what change(s)/modification(s) are being requested as determined by the PI. If this is a multicenter study, only describe change(s)/modification(s) that directly affect this site.

We are modifying the risks to include the possibility of increased pain for 1-2 days following the resolution of the single-injection nerve block if the surgeon/anesthesiologist permitted a continuous peripheral nerve block to be used in that case; and, we are modifying the benefits to include the fact that if the surgeon/anesthesiologist permitted a continuous peripheral nerve block to be used, but the patient choose to participate in the study and forego that technique, that they will not be exposed to the risks inherent in this technique. We are also noting that patients return for a 2-week postop check with their surgeon, and it is at that visit that we will remove the lead. Lastly, we found “principle” misspelled in two locations which we have rectified.

3. Specifically what revision(s) are being made to the Research Plan and why are those revisions being made?

If no changes are being made to the Research Plan, please state the no changes to the Research Plan are required. Otherwise, clearly and specifically describe what revision(s) are being made to the Research Plan and why those revisions are being made.

To add clarity to the consent form for patients who could receive a continuous peripheral nerve block, we are adding to the risks section: "If the patient's surgeon permits a continuous peripheral nerve block (a perineural local anesthetic infusion for 1-2 days following the resolution of their single-injection peripheral nerve block), the participants in this study might have increased pain during this 1-2 day time period should they be randomized to sham or randomized to the active treatment which does not proof effective. Not all surgeons at UC San Diego use continuous peripheral nerve blocks; and those who do use them do so for some patients, but not others (depending on various surgical factors or simply their opinion of the technique). Of note, no other enrolling center offers continuous peripheral nerve blocks to its patients, so this particular risk to study participants is applicable only at UC San Diego (and therefore is included in the informed consent form exclusively for this enrolling center)." We are adding to the potential benefits section: "Lastly, if the participant's surgeon permits continuous nerve blocks and they participate in this study, the participant will not be exposed to the risks of this technique which includes infection (1%), catheter dislodgement (5-10%), and local anesthetic toxicity (very rare)." Lastly, we corrected misspelling of the word "principal" in two locations.

4. Specifically what revision(s) are being made to the consent/permission/assent document(s) and why are those revisions are being made?

If no changes are required to the consent/permission/assent document(s), please state that no changes are required to these documents. Otherwise, clearly and specifically describe what revision(s) are being made to the consent/permission/assent document(s) and why those revisions are being made.

To add clarity to the consent form for patients who could receive a continuous peripheral nerve block, we are expanding the paragraph on the risk of pain to include: "If your surgeon permits a continuous peripheral nerve block, you would have to forgo this continuous block if you are participating in the study and might have increased pain for 1-2 days following when your single-injection nerve block wears off. A continuous nerve block is a technique in which a small tube is inserted at the same time as the initial nerve block, after which local anesthetic is infused using a portable infusion pump and a liter bag of local anesthetic. This technique provides added pain control for 1-2 days longer than a single-injection nerve block, after which the tube is removed at home and patients are then dependent on pain pills for pain relief. If the continuous nerve block is not something that your surgeon will permit (it depends on the surgeon and surgical procedure), then your pain control from the single-injection nerve block will be no different if you are or are not participating in the study." We clarified that nearly all patients return for a 2-week postop check and that's when we remove the lead by adding: "(although nearly all patients return at this time for a 2-week postoperative check with their surgeon regardless of study participation)." Lastly, we added to the potential benefits: "Lastly, if your surgeon permits continuous nerve blocks and you participate in this study, you will not be exposed to the risks of this technique which includes infection (1%), catheter dislodgement (5-10%), and local anesthetic toxicity (very rare)."

5. Will reconsenting/reassenting of subjects be required?

Indicate whether subjects will be reconsented/reassented, and if so, how many subjects. If subject will be reconsented/reassented, please ensure this item includes the procedure that will be used for

reconsenting/reassenting including the timing/completion of the procedures. If enrolled subjects will not be reconsented/reassented, please provide the rationale for not reconsenting/reassenting.

Reconsenting past participants is unnecessary because the potential risk/benefit was discussed during the verbal consent process when it was applicable, and it only applies to the first 1-2 days following block resolution (during postoperative days 2-3). Since none of our study subjects (to which it is applicable) is within 2-3 days of surgery, it is no longer relevant. But, moving forward, the revised UC San Diego ICF should be used as we enroll more and more patients who could receive a continuous peripheral nerve block.

6. Specifically what documents are being submitted with this request?

Specifically outline the documents that should be considered for review in association with the changes/modifications being requested. If study documents have been revised, two copies of a revised documents are required. ***One copy*** *must clearly and specifically* ***highlight all the changes made to the document including additions and deletions by using the track changes function in Microsoft Word (or a similar function in other word processing software)****, and one clean copy of the document must be submitted.*

Research plan and ICF both highlighted and clean for each.

7. Do the requested changes(s)/modification(s) affect risk to subjects, risk management procedures, and/or risk/benefit ratio?

Yes ☐	**No** ☒	
Explain your determination		The risk of pain for the 1-2 days after resolution of the single-injection peripheral nerve block may increase for some participants, but the risks of a continuous peripheral nerve block will be forgone for these same patients (and for patients who participate and are randomized to active stimulation, the pilot data suggests they will have far superior analgesia for 14 days).

8. Do the requested change(s)/modification(s) affect the study in any other way?

Yes ☐	**No** ☒	
Explain your determination		All changes have been described.

Signature			
Principal Investigator		Date:	May 15, 2021

Original (and Final) Statistical Analysis Plan

Dated October 2020, prior to enrollment of the first participant

Statistical Plan and Data Analysis: Implementation Phase [UH3]

Randomized groups will be compared for balance on baseline characteristics using descriptive statistics and the standardized difference (i.e., difference in means or proportions divided by pooled standard deviation). Absolute standardized differences larger than 0.10 will be considered imbalanced and the corresponding variables considered for adjustment in all analyses.[2] Primary analyses will be modified intent-to-treat, such that all randomized patients who receive at least some of the study intervention will be included in the analyses. All patients will be analyzed in the group to which they were randomized. Statistical methods for the Implementation Phase will generally follow the analyses conducted in the Pilot (UG3) phase.

Primary Aim. For Specific Aim 1 we will estimate the treatment effect of PNS versus usual and customary care on pain and opioid consumption using a joint hypothesis testing framework.[3] Specifically, we will conclude PNS is more effective than usual and customary analgesia if it is found to be superior on at least one of pain score or opioid consumption and not worse, i.e., noninferior, on both.

Noninferiority Testing. We will first test for noninferiority of PNS to usual care on each of the two outcomes using 1-tailed tests. The noninferiority deltas will be 1 point (worse) in pain score and 20% higher in opioid consumption. Noninferiority will be assessed at the overall (1-tailed) 0.025 significance level with no adjustment to the significance criterion for testing two outcomes since noninferiority is required on both outcomes – i.e., an intersection-union test. A noninferiority delta of 1 point in pain score is appropriate for between-group comparisons because it is about half the difference that would be considered clinically relevant for intra-subject changes: receiver operating characteristic curve analysis has demonstrated 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.[153,156,177-179]

We will assess noninferiority on pain score using a 1-tailed t-test which incorporates the noninferiority delta of 1 point. The estimated treatment effect for pain score will be derived from a linear mixed effects model with the outcome of patient’s “average” pain score for each day (1,2,3,4,7), with fixed effects for intervention (PNS vs usual care), time (days 1 through 7) and baseline average pain score, and assuming an autoregressive (AR(1)) correlation structure among the measurements on the same patient over time. We will then test for noninferiority with a 1-tailed t-test in which the numerator is the estimated treatment effect from the model minus the noninferiority delta (1), and the denominator is the standard error of the estimated treatment effect.[4] This method will yield results similar to comparing groups on the patient mean across these seven days but is more flexible since it allows for missing data and also directly accounts for the correlation within patient. The model further allows assessing the treatment-by-time interaction, but this will be only of secondary clinical interest. As a sensitivity analysis we will relax the normality assumption and assess the treatment effect (plus test for noninferiority) on pain score over time using a mixed effects quantile regression model [1] in which we consider patient as a random effect, report the treatment effect as the difference in median pain scores, and use the same noninferiority delta of 1.

Cumulative opioid consumption is not typically normally distributed, and usually approximates a log-normal distribution, as in the pilot trial. We therefore plan to assess the treatment effect of PNS versus usual care on the log-transformed cumulative consumption through POD 7

using a linear regression model in which we adjust for any imbalanced baseline variables. The estimated treatment effect (i.e., difference between groups) will then be used in a noninferiority test with null and alternative hypotheses as: H0: $\mu 1 - \mu 2 \geq \log(1.2) = 0.263$ versus HA: $\mu 1 - \mu 2 < \log(1.2) = 0.263$, where $\mu 1$ and $\mu 2$ are the means of log-transformed opioid consumption for PNS and usual care, respectively, and $\mu 1 - \mu 2$ is estimated by the coefficient (i.e., beta) for PNS versus usual care in the regression model. The estimated treatment effect in the model will also be an estimate of the ratio of geometric means for the two groups, assuming data for each group is log-normal with similar coefficient of variation between groups.

Superiority Testing. If noninferiority is found on both pain and opioid consumption we will test for superiority on each outcome using 1-tailed tests in the same direction. For superiority testing, since superiority on either outcome would be sufficient to reject the joint null hypothesis (i.e., a union-intersection test), we will control the type I error at 0.025 across the 2 outcomes by using a Bonferroni correction and using 0.025/2=0.0125 as the significance criterion.

Secondary Outcomes. We will assess the treatment effect on secondary outcomes using appropriate statistical methods. We will use a linear mixed effects model to assess the treatment effect over time for additional outcomes measured at days POD 1-7 (1, 2, 3, 4, 7), as in the primary analysis, including worst pain and the Defense and Veterans Pain Rating Scale; similarly we will assess the treatment effect on total severity score and total interference score at days 3 and 7. As sensitivity analyses we will also use a generalized ordinal regression model for each of these outcomes. For outcomes analyzed at a single time point (days 11, 18; months 1, 4, 12) we will use 2-sample t-test or Wilcoxon rank sum test for physical and functioning as measured by the Brief Pain Inventory (Hypothesis 3), chi-square analyses and t-test of Wilcoxon rank sum test for incidence and intensity of chronic pain, respectively (Hypothesis 4), and Wilcoxon rank sum test for quality of life measure by the World Health Organization Quality of Life-BREF Instrument. Analogous regression models would be used, as needed, to adjust for baseline imbalance.

Study-wide Type I error control. We will use a parallel gatekeeping procedure [1,5,6] to control the study-wide type I error at 0.05. For this procedure we *a priori* prioritize the study outcomes into 10 ordered sets, as given in **Table 5**. 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 0.025 [for each direction of interest; primary outcomes being 1-sided and all others 2-sided] 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 or Holm-Bonferroni correction) will be used as appropriate to control the type I error at the appropriate level.

Table 5. Ordered sets for Parallel Gatekeeping Procedure

Ordered Set #	Outcome(s)	Measurement Timing ^

1	Primary outcomes Average pain, opioid consumption	POD 1-7
2	Worst pain score	POD 1-7
	DVPRS	POD 1-7
3	BPI interference subscale	POD3, POD7
4	Worst pain	POD 1-11
	DVPRS	"
	Average pain	"
5	Worst pain	Months 4, and 12
6	Worst pain	POD 18
	DVPRS	"
	Average pain	"
7	Worst pain	Month 1
	DVPRS	"
	Average pain	"
8	Worst pain	Month 4
	DVPRS	"
	Average pain	"
9	BPI interference subscale	Months 1, 4, and 12
	WHO-DAS	"

* Additional outcome measures and time points, such as least and current pain levels (from the BPI) will be considered exploratory and not compared statistically
^ throughout, POD 1 refers to POD 0 after PACU through POD1

Assessment of treatment effect heterogeneity. There is little relevant prior experience with the study intervention in the patient population of the proposed investigation, so it is not known whether either sex would interact with the treatment effect. Therefore, in accord with the Human Subjects recommendations, we will assess the treatment effect of PNS on the primary outcomes of interest (pain score, opioid consumption) within levels of sex, and asses the interaction. In addition, we will assess treatment effect heterogeneity across within anatomical locations across the various lead insertion sites, across types of surgical procedures, and across levels of other baseline characteristics as listed below. We will assess the treatment-by-covariate interaction in the appropriate statistical model (i.e., the model used in the primary analyses). We will report the treatment effect within levels of each factor whether or not a significant interaction ($P<0.10$) is found.

We will assess treatment effect heterogeneity across levels of the following variables:

- sex (male, female)
- military (BAMC, WAMC, WRNMMC and NMCSD) vs. civilian (Cedars and UCSD)
- baseline average NRS (< 4, ≥ 4)
- baseline DVPRS (< 5, ≥ 5)
- baseline interference scale of the BPI < 20, ≥ 20)
- duration of surgery (< 90 min, ≥ 90 min)
- bupivacaine vs. ropivacaine (for the initial peripheral nerve block)
- saphenous nerve block (versus not) for lower extremity surgeries
- surgical site (shoulder, foot, ankle)
- surgical procedure (rotator cuff repair, hallux valgus, ankle arthrodesis, ankle arthroplasty)
- for brachial plexus leads: lead positioning (posterior to roots, superior trunk, middle trunk, other)
- for sciatic leads: lead positioning (medial, lateral)
- for sciatic leads: lead positioning (anterior, posterior)

Missing Data. While based on our UG3 results very little missing outcome data is expected, any missing data will be summarized overall and by randomized group along with the known/presumed etiology of the absence. If the missing data for an analysis appear to be missing at random for an outcome which is only designed to be measured once for a patient, we will assign values using multiple imputation (using 5 imputed datasets, and aggregating results across them) in which all other available baseline and outcome data will be used to predict the missing data point(s).[7] For longitudinal outcomes such as the primary outcome pain score, if data appear largely to be missing at random and with comparable frequency between groups, and all patients have at least some non-missing data, we will ignore the missing data for the primary analysis. If there would be a non-trivial amount of missing data (e.g., > 10 percent missing) for a particular outcome, and the data did not appear in general to be missing at random, we would consider implementing a pattern mixture model approach in which randomized groups are compared on outcome within subgroups defined by the pattern of missing data, for e.g., with results then aggregated across patterns.

Interim Analyses for Efficacy and Futility. A substantive difference from the planning phase is that in the full trial we will conduct interim analyses to assess efficacy and futility at each 25% of the maximum planned enrollment. We will use a group sequential design with gamma spending function[8] and gamma parameters of -4 (quite conservative) for efficacy and -2 (moderately conservative) for futility (**Figure 14**). Assuming the alternative hypotheses were true, the probability of crossing a boundary for either efficacy (mainly) or futility at the first through fourth looks would be 0.07, 0.36, 0.75 and 1.0, respectively.

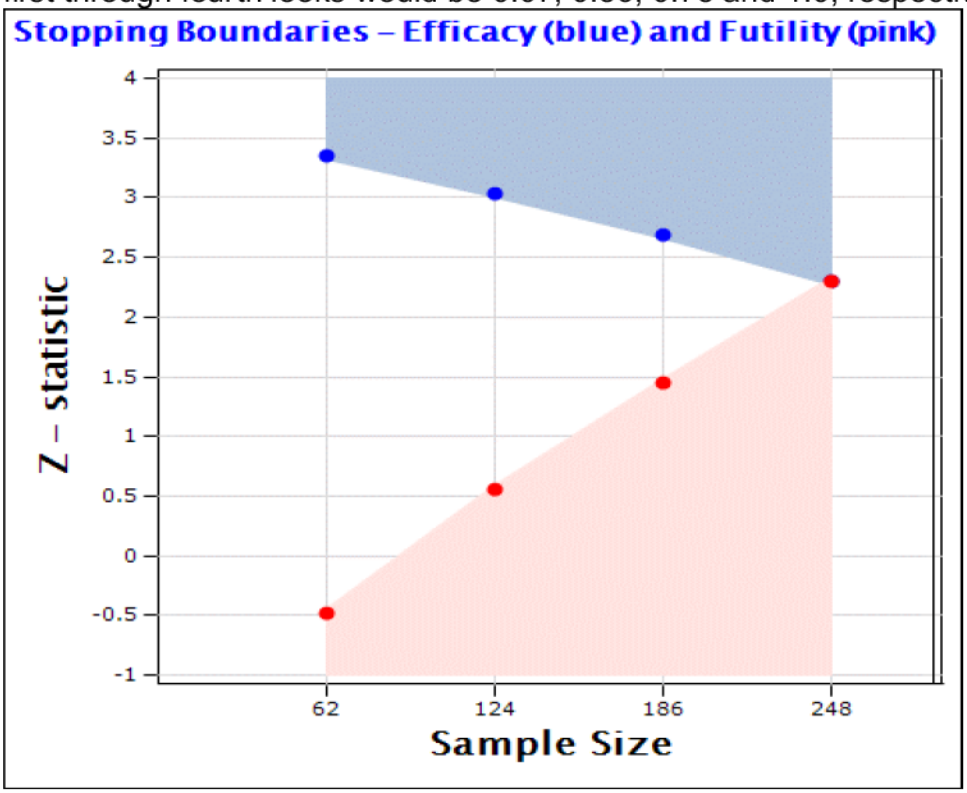


Figure 14. Stopping boundaries for 1-tailed tests for superiority for either pain score or opioid consumption. Blue region indicates superiority (reduced opioid consumption or pain score) and pink region indicates futility (lack of superiority). Z-statistic represents strength of evidence against the null hypothesis, either ratio of means or difference in means, each divided by standard error.

Sample size Justification and Considerations [UH3 Implementation Phase]. Sample size parameters for the implementation phase were informed from our estimates in the planning phase which included N=31 Stimulation and N=34 Placebo patients. For this full trial we choose a sample size which will maintain an overall 90% power at the 0.025 significance level (since 1-tailed tests) to claim the intervention more effective than the control on postoperative opioid requirements and pain as measured by NRS pain score in our joint hypothesis testing framework. We plan the study to have 90% power to detect superiority on either outcome and at least noninferiority on both. Power for the joint hypothesis testing will be driven by superiority tests since superiority is needed for at least 1 of the 2 outcomes.

Opioid consumption. For cumulative opioid consumption through POD 7 our pilot study data had a coefficient of variation (CV) of 136% (mean (SD) of 17.9 ± 24.3 mg) for the Stimulation patients, 109% (mean (SD) of 17.9 ± 24.3 mg) for Placebo patients, and 142% (mean (SD) of 48 ± 68) overall. The ratio of geometric means (97.5% CI) in the pilot study was 0.20 (0.07, 0.57), for an 80% observed relative reduction, with confidence interval including as small as a 43% reduction.

For the implementation phase we conservatively assume a coefficient of variation of 150% for each group in opioid consumption through 7 days and plan for at least a 40% relative reduction. With these assumptions we will need a total of N= 228 patients to have 90% power to detect a relative reduction of 40% or more (i.e., ratio of geometric means of 0.60 or stronger) in mean opioid consumption at the overall 0.025 1-tailed significance level (0.0125 for each of the two 1-tailed tests for superiority). We use 1-tailed tests here because in the analysis we will only test for superiority after noninferiority of stimulation to placebo has been found. **After adjusting for interim analyses the required maximum total sample size is 250 (125 per group).**

With a sample size of 250 total we would further have 90% power to detect noninferiority in opioid consumption using a noninferiority delta of 1.2 for the ratio of geometric means after assuming a coefficient of variation of 150% and a true ratio of means of 0.75 or more. For a scenario with equal means (ratio of 1.0) we would only have about 25% power to detect noninferiority.

Pain score. In our pilot study we observed a reduction in the mean (97.5%CI) of average pain score of -1.7 (-2.5, -0.85) in Stimulation versus Placebo in the linear mixed effects model across POD1-7. We also observed a within-group standard deviation of pain score ranging from 1.1 to 2.6 across POD 1-7, and values of 1.1 for Stimulation and 1.7 for Placebo for the patient mean across those days. Finally, we observed an intraclass correlation of 0.47 for pain score in the linear mixed effects model across POD1-7. We used these estimates below in assessing the power and sample size for average pain score the implementation phase.

A difference between groups of 1.0 in average pain score is the smallest that would be considered clinically important. With a maximum total sample size of **250** we will have 95% power at the overall 0.025 1-tailed significance level (0.0125 for each of the two 1-tailed tests for superiority) to detect a difference of 1.0 or more between Stimulation and Placebo on mean pain score conservatively assuming a SD of 2.5 for pain score at each day (1, 2, 3, 4, 7) and ICC of 0.50.

Power for Subgroup Analyses. A main difference from the Planning/Pilot phase is that in this full trial we will have sufficient data to conduct the subgroup analyses and we also will have power to detect smaller treatment effects. For example, with 250 total patients, we would have about 90% power to detect a ratio of geometric means of 0.50 or stronger (smaller than observed in the pilot study) in subgroups of size N=125.

The overall significance level will be 0.025 for the primary aim when assessing noninferiority and superiority in 1-tailed tests, and 0.05 when assessing for superiority on secondary outcomes in both directions. SAS statistical software (Cary, NC) will be used for all analyses, and East 6.0 (Cytel, Inc. Cambridge, MA) for interim monitoring and sample size calculations.

Summary of Changes, Statistical Analysis Plan

Final statistical analysis plan did not differ from the original—there were no revisions requested from the IRB. However, there were 2 differences from what was originally planned vs conducted:

1. The first is in the criterion for deciding balance at baseline. Protocol says "Absolute standardized differences larger than 0.10 will be considered imbalanced and the corresponding variables considered for adjustment in all analyses.[2]" In the submitted Appendix, the statistician wrote that we used a less stringent criterion of ASD > 0.248, citing the Austin 2009 paper, and explained that this was the better choice for a smaller trial like this.

   However, in retrospect the statistician thought it would have been better to directly acknowledge that we made a conscious change from the initial protocol, instead of saying "inadvertently" or "incorrectly". He explains that it is fairly common to make statistical changes based on something observed in the data (e.g., the observed distribution of an outcome does not meet the assumed assumptions). But the change was actually made without looking at the data – just because that is what we now use for all small to moderately sized trials.

2. In Secondary outcomes in the Protocol we say: "As sensitivity analyses we will also use a generalized ordinal regression model for each of these outcomes." In fact we used a slightly different model for this sensitivity analysis because it was more straightforward and easier to interpret for the audience - a proportional odds GEE model. We didn't comment on that difference because it was quite similar – both models are appropriate for ordinal data, and that was the idea — to conduct an analysis that did not assume that the ordinal data was normally distributed. Manuscript: "To ensure robustness, sensitivity analyses for secondary measures employed generalized estimating equations with a proportional odds model."

University of California, San Diego
Consent to Act as a Research Subject

Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation:
A Non-Pharmacologic Alternative for the Treatment of Postoperative Pain

Who is conducting the study, why you have been asked to participate, how you were selected, and what is the approximate number of participants in the study?
Dr. Brian Ilfeld and colleagues are conducting a research study to determine if the effects of applying a small amount of electrical current near the nerve going to your limb having surgery will provide pain control following your surgical procedure. You have been asked to participate in this study because you are scheduled to undergo surgery that frequently results in moderate or severe pain. The study will investigate if electrical stimulation delivered through a tiny wire placed near the nerve innervating your surgical limb will decrease pain following surgery. A small electrical stimulator will be used to produce the electricity. The study is being conducted at the University of California San Diego Medical Center hospitals and is funded by the Department of Defense. There will be approximately 200 participants at this site and approximately 400 participants at all sites.

Why is this study being done?
The purpose of this study is to determine if the effects of applying a small amount of electrical current near the nerve going to your limb having surgery will provide pain control following your surgical procedure.

What will happen to you in this study and which procedures are standard of care and which are experimental?
If you agree to be in this study, the following will happen to you:

1. You will have a tiny wire called an “electrical lead” inserted through a needle and placed 0.5-2.0 cm away from the nerve that goes to your limb having surgery. First, the area where the lead will be placed is washed with a special solution to cleanse the area, then the skin is numbed with a small amount of local anesthetic, after which a physician will insert a needle with the lead to lie near your nerve using “ultrasound”—a machine that allows us to look inside your body without any radiation exposure. A small amount of electricity will be passed through the lead and you will feel what most people describe as a gentle “massage” in your limb. The needle will be removed leaving the lead near your nerve. A dressing will be placed to hold the lead in place and keep it sterile. Your skin sensation and muscle strength will be tested.
2. You will then have a peripheral nerve block administered using ultrasound to guide a needle through your skin to the nerve that goes to your surgical limb. Then, local anesthetic—numbing medicine—will be injected through the needle to surround your nerve. This will make your limb numb for approximately 8-12 hours. This will be done whether or not you participate in the study.
3. You will then continue with your surgery—nothing will be different than if you were not participating in the study.

4. Following surgery, you will be assigned by chance to a study group. Your chance of being assigned to each group is 50%, or 1 in 2. Neither you nor the researchers can choose the group to which you will be assigned. If you are in Group 1, a stimulator—a device that delivers a small amount of electricity—will be hooked up to your lead and turned on, passing electrical current through the lead. If you are in Group 2, a stimulator that does not actually deliver any electrical current will be hooked up to your lead and turned on.
5. When you are ready to leave the recovery room, you will be discharged with the stimulator and lead. You will be discharged with a prescription for pain pills that help to take away pain—this is the same whether or not you participate in the study.
6. Depending on the timing of your surgery and your availability, you might receive a call from the investigators to review the stimulator instructions after you return home on the same day of your surgery. You will be called following surgery by an investigator and asked questions related to your surgical pain and the stimulator and lead 1, 2, 3, 4, 7, and 11 days following surgery. You will be given the contact information for an investigator so that you can reach someone with any questions or concerns at all times of day or night while your lead is in place.
7. After 14 +/-3 days a physician will remove the electric lead and stimulator at the hospital or clinic. You will be called the 18th day after surgery as well as 1, 4 and 12 months following surgery.

How much time will each study procedure take, what is your total time commitment, and how long will the study last?

Putting in the lead will take about 30 minutes; and, hooking up the stimulators, testing the leads, and teaching you how to use/care for the system will take about 30 more minutes. In the recovery room after surgery, the stimulator and lead will be tested as described above, which will take about 10 minutes. In most cases this will not delay your discharge as most patients spend at least this much time in the recovery room following surgery regardless of study participation. The phone calls that you will receive following discharge will take 5-15 minutes each, but you will need to return to the healthcare facility after 14 days to have the lead removed (although nearly all patients return at this time for a 2-week postoperative check with their surgeon regardless of study participation). You will be participating in the study for a total of 12 months, since the final phone call will be made 12 months following surgery.

What risks are associated with this study?

All research involves some risk, and there may be some unknown risks that are currently unforeseeable. You will be informed of any significant new findings. You will be exposed to the following additional potential risks:

1. Infection. There is the potential risk of infection since you will have a lead remain in place for 14 days. If this were to occur, it would be treated by removal of the lead and then medicine to treat the infection (antibiotics).

2. Lead breakage. Sometimes the lead breaks when it is being removed (in about 8 out of 100 leads). If this occurs, the part of the lead that remains in your body will be left in place unless it causes you discomfort. To date, no lead that has broken off has caused a patient discomfort or harm; and it is safe to have magnetic resonance imaging (MRI) with a small broken lead in place.

3. The lead could fall out. If this occurred, you would have the option of having it replaced at the earliest time possible.

4. Nerve injury. Because the needle to place the lead—and the lead itself—are placed at least 1 centimeter (about half an inch) away from your nerve, there is very limited chance of having some kind of nerve injury. However, it remains a possibility.

5. During lead insertion, there is the risk of bleeding due to the insertion needle. If this was to happen, simply holding pressure on the site ultimately stops the bleeding.

6. Skin irritation. The lead is kept clean and in place with a bandage. Some patients have skin irritation due to the adhesive on the bandage.

7. Lead migration. Although it has not been reported to date, there is the possibility that the lead tip will move during the 14 days that it is in place. If this was to occur, any pain control that you were receiving due to the lead and stimulator would presumably decrease.

8. Pain. There is the possibility of pain during lead insertion, during use, or upon withdrawal. If your surgeon permits a continuous peripheral nerve block, you would have to forgo this continuous block if you are participating in the study and might have increased pain for 1-2 days following when your single-injection nerve block wears off. A continuous nerve block is a technique in which a small tube is inserted at the same time as the initial nerve block, after which local anesthetic is infused using a portable infusion pump and a liter bag of local anesthetic. This technique provides added pain control for 1-2 days longer than a single-injection nerve block, after which the tube is removed at home and patients are then dependent on pain pills for pain relief. If the continuous nerve block is not something that your surgeon will permit (it depends on the surgeon and surgical procedure), then your pain control from the single-injection nerve block will be no different if you are or are not participating in the study.

9. There is the risk of loss of confidentiality. The following procedures will be done to maintain confidentiality: written, paper forms will be kept in a locked medical office and the locked Investigational Pharmacy's files. Computerized records containing personal health information will be stored on password-protected and encrypted computers.

What are the alternatives to participating in this study?
The alternative to participation in this study is to decline participation and continue with your surgery without change.

What benefits can be reasonably expected?
If you agree to take part in this study, you may or may not receive any direct medical benefit. However, you may experience a decrease in the incidence (if it occurs at all), frequency (how often it occurs), duration (how long each episode lasts), and intensity (how much it hurts) of pain immediately after surgery and chronic pain. In addition, by being part of this study, you may possibly help future patients by helping us to determine if the lead and stimulation system will decrease pain following surgery and the need for pain medicine. Lastly, if your surgeon permits continuous nerve blocks and you participate in this study, you will not be exposed to the risks of this technique which includes infection (1%), catheter dislodgement (5-10%), and local anesthetic toxicity (very rare).

Can you choose to not participate or withdraw from the study without penalty or loss of benefits?
Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without penalty or loss of benefits to which you are entitled. If you decide that you no longer wish to continue in this study, you are free to do so at any time during your participation period. If you withdraw, your lead will be removed if it is still in place, and you will not be contacted regarding the study in the future. Please contact the Principal Investigator, Dr. Brian Ilfeld at 619-543-6222.

Can you be withdrawn from the study without your consent?
You may also be withdrawn from the study if the investigator feels it is in your best interest or for other study-related purposes. You may also be withdrawn from the study if you do not follow the instructions given you by the study personnel. If you withdraw, your lead will be removed if it is still in place, and you will not be contacted regarding the study in the future.

Will you be compensated for participating in this study?
There is no financial compensation for participating in the study.

Are there any costs associated with participating in this study?
There are no additional costs associated with participating in the study other than any transportation costs and parking charges when you return to have your lead removed two weeks after surgery.

What if you are injured as a direct result of being in this study?
If you are injured as a direct result of participation in this research, the University of California will provide any medical care you need to treat those injuries. The University will not provide any other form of compensation to you if you are injured. You may call the Human Research Protections Program Office at (858) 246-4777 for more

information about this, to inquire about your rights as a research subject or to report research-related problems.

What about your confidentiality?
Research records will be kept confidential to the extent allowed by law. Paper copies of study documents will be kept in locked medical offices. Any digitized records containing personal health information will be stored as password-protected and encrypted files. Research records may be reviewed by the UCSD Institutional Review Board.

The original, hard-copy signed informed consent forms and case report forms from participants at UCSD will be stored within the principals investigator's locked office, where they will remain for at least 7 years. These hard copies will not be mailed. Data will be uploaded and stored in one location: the central servers of Department of Outcomes Research at the Cleveland Clinic. 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. Databases are protected through electronic measures: 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. Only the research monitor at UCSD, the principal investigator, and a data entry technician will have access to the electronic database. The electronic data will remain within the Department of Outcomes Research for 7 years following study completion. The USAMRMC (United States Army Medical Research and Materiel Command) is eligible to review study records at any time.

Sharing study results. Following study completion, you 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, which means that you could not be identified personally by someone looking at the study data; your information would be anonymous.

Your research information may be disclosed to the local and University of California San Diego Institutional Review Boards and their research review staff, the Department of Defense (specifically, the United States Army Medical Research and Materiel Command), a data safety monitoring board headed by a medical monitor (Steven Shafer, MD) who oversees this study, and the U.S. Food and Drug Administration. Otherwise, the information may be maintained in a confidential manner indefinitely, but for at least seven years. The Institutional Review Board is a committee whose job is to protect the safety and privacy of research subjects.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

This study is being funded by the United States Department of Defense.

Who can you call if you have questions?
Dr. Brian Ilfeld, and/or his colleagues, has explained this study to you and answered your questions. If you have other questions or research-related problems, you may reach Dr. Brian Ilfeld at 619-543-6222.

You may call the Human Research Protections Program Office at (858) 246-4777 to inquire about your rights as a research subject or to report research-related problems.

Your Signature and Consent:
You have received a copy of this consent document and a copy of the "Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____ _____
Subject's signature Date

NAME OF PERSON OBTAINING CONSENT (Please Print):

_____
Printed Name of Person Obtaining Consent

_____
Signature of Person Obtaining Consent Date