Official Title: A Device Enabling Both Local Anesthetic Delivery and Neuromodulation for Postoperative Analgesia: A Feasibility and Randomized Pilot Study

NCT: 06818708

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A Randomized, Single-Blinded, Sham-Controlled Study Evaluating the Efficacy and Safety of RELAY, a Device Enabling Both Local Anesthetic Delivery and Neuromodulation for Postoperative Analgesia, in Participants Having Shoulder or Foot Surgery Following a Single Arm Training Run-In

Protocol Number: 810455

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Principal Investigator: Brian M. Ilfeld, MD, MS

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Cover page, funding information.	Funding information is revised to "Gate Science, the study sponsor is paying UC San Diego to conduct this research study."	To clarify funding information.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	A Randomized, Single-Blinded, Sham-Controlled Study Evaluating the Efficacy and Safety of RELAY, a Device Enabling Both Local Anesthetic Delivery and Neuromodulation for Postoperative Analgesia, in Participants Having Shoulder or Foot Surgery Following a Single-Arm Training Run-In.
Study Description:	This is a single-center, sham-controlled study to investigate the efficacy and safety of RELAY, a device that enables the delivery of both local anesthetic and neuromodulation (peripheral nerve stimulation) to treat postoperative pain. RELAY is comprised of a basic catheter-over-needle device to allow administration of a single-injection of local anesthetic via the needle (or catheter) followed by a perineural local anesthetic infusion via the remaining catheter (when desired). Subsequent to the local anesthetic administration, instead of removing the catheter as with all previous continuous peripheral nerve block equipment, electric current may be delivered via the same catheter for up to a total of 28 days. This is potentially paradigm shifting because it would allow an anesthesiologist to deliver (1) a single-injection peripheral nerve block; (2) a continuous peripheral nerve block; and (3) neuromodulation using a single device that can theoretically be placed in the same amount of time required for a single-injection peripheral nerve block. Instead of providing fewer than 24 hours of postoperative analgesia, up to 28 days of pain control could be delivered without disruption of the existing practice patterns. Following a training run-in period, the randomized single blind sham-controlled part of the study will commence. The purpose of the training run-in period is to ensure that RELAY can be safely placed next to a target nerve, successfully programmed and induce peripheral nerve block and neuromodulation based on the instructions for use. This will ensure familiarity with the device prior to the randomized portion of the study. The training period will consist of up to 20 participants (~ 5 to 10 catheter lead insertions per anesthesiologist) across at least two different surgical procedures. It is anticipated that during the training run-in phase, the successful deployment of the RELAY system will be achieved 80% or more of the time. If less than 80% is achieved, the study will not proceed to the randomized portion. A brief study report will be submitted to the FDA prior to initiating the randomized portion. RELAY deployment success will be defined as a successfully placed catheter/lead as evidenced by sensory changes in the distribution of the target nerve with (1) electrical stimulation eliciting paresthesia and (2) inducing a conduction nerve block with injection of local anesthetic injection leading to either decreased or absent sensation to cold with alcohol swab. The randomized portion will include 40 participants (with up to 10 additional participants to account for drop-outs) randomized (1:1) to the experimental and sham arms, respectively. A futility analysis will be performed once 20 participants have been randomized and data through post-operative Day 7 are available. The following two criteria must be achieved to move forward: 1) RELAY deployment success in the lead/catheter insertion of ≥ 85% in RELAY participants, and 2) a conditional power

	(Cp) of ≥30% for the primary efficacy endpoint. Of note, a standardized effect size of 0.49 would not meet criteria to continue. There will be no stopping for early efficacy.
Objectives/ Endpoints	The primary objective of the proposed research study is to assess postoperative analgesia that extends beyond the duration of the local anesthetic interventions to prepare for a subsequent pivotal definitive clinical trial with the RELAY device compared to sham control. **Primary endpoint:** Difference in the **average daily pain intensity** for Days 1-7 as measured with the Numeric Rating Scale (NRS) within the Brief Pain Inventory (BPI) via the RELAY device compared to sham control. • ***Hypothesis 1:*** Neuromodulation with the RELAY device will decrease ***average pain intensity*** for Days 1-7 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (as measured with the NRS within the BPI). **The key secondary objectives are:** 1) To estimate the effect on **opioid consumption** of neuromodulation via the RELAY device as compared to sham control **Key secondary endpoint 1** (hierarchical: tested for significance only if the primary endpoint achieves significance at alpha 1-sided <0.025): Difference in the cumulative opioid use (oxycodone equivalents) for Days 1-7 via the RELAY device compared to sham control. • ***Hypothesis 2:*** Neuromodulation with the RELAY device will decrease ***opioid consumption*** within the week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (measured in oxycodone equivalents), as measured both with daily and cumulative opioid consumption within the first postoperative week). 2) To estimate the effect on ***physical and emotional functioning*** of neuromodulation via the RELAY device as compared to sham control **Key secondary endpoint 2** (hierarchical: tested for significance only if the primary endpoint and key secondary endpoint 1 both achieve significance at alpha 1-sided <0.025): Difference in BPI interference subscale on Day 3 as measured with the NRS within the BPI Inventory via the RELAY device compared to sham control. • **Hypothesis 3:** Neuromodulation with the RELAY device will decrease pain's ***interference in physical and emotional functioning*** within the week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (as measured with the Interference Subscale of the BPI). **Other Secondary Endpoints to include:** • Interference in physical and emotional functioning (as measured with the Interference Subscale of the BPI) on Post-op Day 7 • Opioid use (oxycodone equivalents) on Post-op Days 1, 2, 3, 4, 7, 8 and 14 • Awakenings due to pain on Post-op Days 1, 2, 3, 4, 7, 8 and 14

<table>
<tr><td></td><td>

Daily Pain intensity (“average” and “worst” NRS) on Post-op Days 1, 2, 3, 4, 7, 8, 14
Daily Pain intensity (“current” and “least” NRS) on Post-op Days 3 and 7
Frequency, pulse duration, amplitude, and anode (proximal vs distal) will be recorded at baseline; amplitude during postoperative Days 1, 2, 3, 4, and 7
Masking assessment on Post-op Day 1 (randomized period only)

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<tr><td>Post-Enrollment Assessments</td><td>
Summary of post-enrollment assessments (color added for clarity)
<table>
<tr><th>Postoperative Day:</th><th>1</th><th>2</th><th>3</th><th>4</th><th>7</th><th>8</th><th>14</th></tr>
<tr><td>Opioid consumption</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr>
<tr><td>Average Pain [Numeric Rating Scale; as part of the Brief Pain Inventory]</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr>
<tr><td>Worst Pain [Numeric Rating Scale; as part of the Brief Pain Inventory]</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr>
<tr><td>Brief Pain Inventory</td><td></td><td></td><td>•</td><td></td><td></td><td></td><td>•</td></tr>
<tr><td>Awakenings from sleep due to pain</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td><td>•</td></tr>
<tr><td>Masking Assessment (randomized period only)</td><td>•</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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<tr><td>Study Population</td><td>
There will be approximately 70 participants.

Inclusion criteria:

Adult participants of at least 18 years of age
Undergoing a rotator cuff repair, total shoulder arthroplasty, hallux valgus correction or ankle arthroplasty/arthrodesis
Planned single-injection peripheral nerve block(s)
An Android or Apple smartphone able to download the Gate Keeper controller app

Exclusion criteria:

Chronic opioid or tramadol use (daily within prior 2 weeks and duration > 4 weeks)
Neuro-muscular deficit of the surgical limb
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 of infection
Implanted spinal cord stimulator, cardiac pacemaker/defibrillator, deep brain stimulator, or other implantable neurostimulator whose stimulus current pathway may overlap
History of bleeding disorder
Antiplatelet or anticoagulation therapies other than aspirin
Allergy to skin-contact materials (occlusive dressings, bandages, tape etc.)
Incarceration

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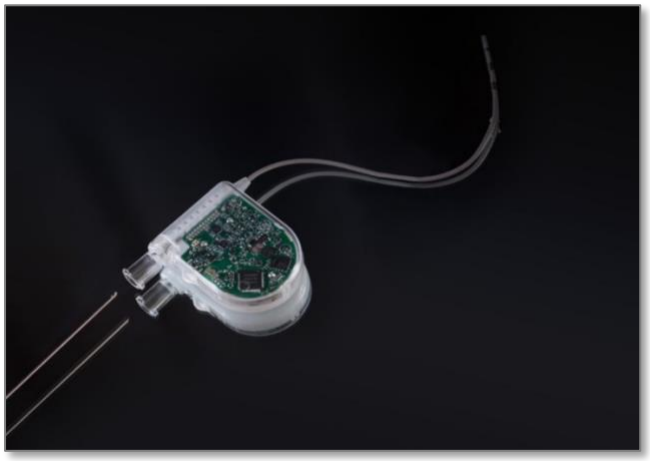
	9. Pregnancy 10. Moderate pain (NRS > 3) in an anatomic location other than the surgical site 11. Anxiety disorder 12. History of substance misuse 13. Inability to communicate with the investigators 14. Inability to contact the investigators during the treatment period, and vice versa (e.g., lack of telephone access) 15. Allergy to amide local anesthetics 16. Morbid obesity (body mass index > 40 kg/m^2)
Phase:	Not applicable to this investigation involving a medical device (as opposed to a medication)
Description of Sites/Facilities Enrolling Participants	U.C. San Diego Clinical and Translational Research Institute and hospitals (including the ambulatory surgical centers)
Description of Study Intervention	The RELAY system combines a catheter-over-needle to permit ultrasound-guided percutaneous insertion with the tip adjacent to a peripheral nerve or plexus, followed by needle removal which leaves the catheter in situ to deliver a bolus of local anesthetic (if desired) and subsequent perineural local anesthetic infusion (if desired). The catheter also has 3 integrated electrodes to enable neuromodulation using the integrated pulse generator and battery (figure below).  Participants will have standard external monitors placed and oxygen delivered by facemask or nasal cannula. The peripheral nerve block site(s) will be cleansed with chlorhexidine gluconate and isopropyl alcohol. Intravenous sedation/analgesia with midazolam and/or fentanyl will be titrated for patient comfort as is standard for peripheral nerve block administration. ***The nerves treated will include the sciatic proximal to the popliteal crease for foot surgery and the brachial plexus for shoulder surgery***. The target nerve(s) will be visualized with ultrasound using a transverse cross-sectional (short axis) view and a skin wheal of local anesthetic will be raised inferior to the transducer to anesthetize the skin and then the track towards the target.

Treatment group allocation (randomization). Participants in the training run-in period will all receive active neuromodulation. Participants in the randomized portion will be randomized (1:1) to one of two possible treatments groups:

- ***Neuromodulation (Active)***
- ***Sham (Control)***

Randomization will be stratified by anatomic location (shoulder and foot/ankle surgery) in a 1:1 ratio and in blocks of 2. Computer-generated randomization lists will be created by the UC San Diego Investigational Drug Service and the allocation provided to the investigators *via* sequential, opaque envelopes.

Pulse generators are available that are capable of either (1) passing electrical current; or (2) not passing electrical current. Importantly, these 2 modes (active and sham) are indistinguishable in appearance, and therefore investigators, participants, and all clinical staff will be masked to treatment group assignment, with the only exception being the unmasked individuals who insert the RELAY and program the stimulator.

The RELAY system with the integrated needle will be inserted adjacent to the target nerve with an in-plane approach. Dextrose 5% in water (1-20 mL) will be injected via the needle to open a space around the target nerve(s), the catheter advanced, and the needle subsequently withdrawn.

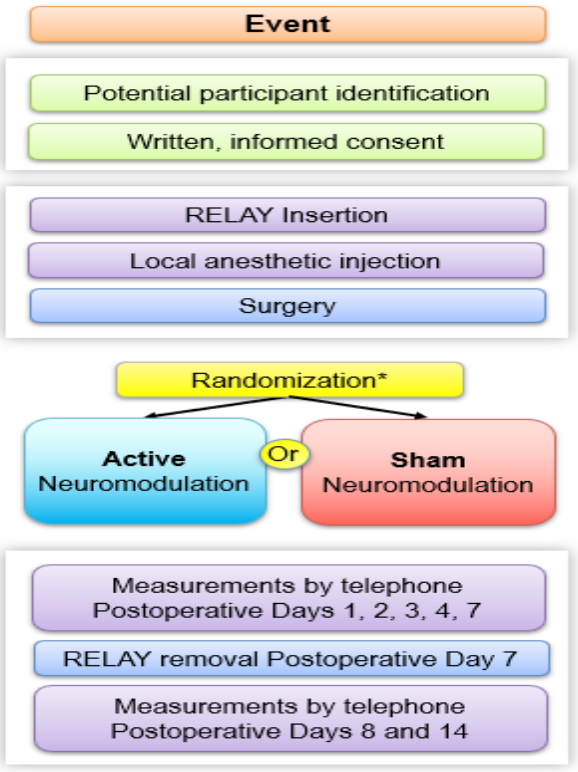
Active (neuromodulation) group. For participants receiving **active** (neuromodulation) treatment, electrical current will be introduced with increasing intensity via each of the anode electrodes to optimize participant's perceived stimulation (control provided by the Gate Keeper app from an investigator's phone or tablet). Accurate lead placement will be confirmed with subject reports of comfortable sensations over the surgical site without eliciting muscle contractions. The minimum threshold and maximum comfortable amplitudes will be determined along with the optimal frequency, pulse duration, and anode/cathode. Starting from the lowest possible current the current will be increased until a participant states that they feel a "buzzing" sensation (some describe it as a "comfortable massage"). That is the minimal sensed current. The current will then continue to be increased with instruction to the participant to let the investigator know when it starts to be less comfortable—and to stop the investigator before it hurts. That is the maximum comfortable current. The stimulator will then be set to deliver the minimum threshold amplitude and turned off for surgery.

Sham (control) group. For participants receiving **sham** treatment, electric current will not reach the anodes, but the investigators will connect the RELAY to the Gate Keeper app just as with the active group and set the parameters as follows: anode (distal), cathode (proximal), frequency (100 Hz), pulse duration (100 µs), and amplitude (5 mA).

Local anesthetic for active and sham groups. Local anesthetic (10 mL of lidocaine 2% with epinephrine) will be injected with negative aspiration every 3 mL and resulting sensory block confirmed to ensure accurate catheter tip placement. Following block confirmation (sensory deficits in the expected nerve distributions), the RELAY system will be affixed with both surgical adhesive (2-Octyl 2-cyanoacrylate) at the entry site and a chlorohexidine-impregnated occlusive dressing. Subsequently, 10 mL of bupivacaine 0.5% with epinephrine will be injected negative aspiration every 3 mL

	along with a supplemental single-injection saphenous nerve block for foot/ankle surgery. Intraoperatively, surgeons will be permitted to infiltrate the surgical area with long-acting local anesthetic as their common practice dictates. Postoperatively, the stimulators will be connected to participants' phones and turned on. For the training run-in period, if a patient's surgeon requests a postoperative continuous peripheral nerve block, a ropivacaine 0.2% infusion will be provided per standard UC San Diego protocol. After 7 days, participants in both the active and sham groups, themselves or their caretaker will remove the occlusive dressing and withdraw the catheter (and integrated electrodes) with gentle traction and rotation at home. The devices are single-use and disposable.
Study Duration:	Approximately 12 months
Participant Duration:	Approximately 2 weeks

1.2 SCHEMA



*Randomization not applicable to the training run-in period. All participants in the training run-in period will receive Active Neuromodulation

1.3 SCHEDULE OF ACTIVITIES (SOA)

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

Postoperative Day:	0	1	2	3	4	7	8	14
Written informed consent	•							
RELAY insertion	•							
Local anesthetic injection	•							
Surgery	•							
Randomization (randomized period only)	•							
Opioid consumption		•	•	•	•	•	•	•
Average Pain [Numeric Rating Scale; as part of the Brief Pain Inventory]		•	•	•	•	•	•	•
Worst Pain [Numeric Rating Scale; as part of the Brief Pain Inventory]		•	•	•	•	•	•	•
Brief Pain Inventory				•		•		
Awakenings from sleep due to pain		•	•	•	•	•	•	•
Masking Assessment (randomized period only)		•						

2 INTRODUCTION

2.1 STUDY RATIONALE

Postoperative pain remains undertreated with inadequate analgesic options. Opioids have well-known limitations for both individuals and society; single-injection and continuous peripheral nerve blocks provide intense analgesia but are limited in duration to 24-72 hours; and current neuromodulation options—with a duration measured in weeks and not hours—are prohibitively expensive and require an additional procedure. One possible solution is a device currently under investigation to treat postoperative pain. The RELAY system (Gate Science, Moultonborough, New Hampshire) is comprised of a basic catheter-over-needle device to allow administration of a single-injection of local anesthetic via the needle (or catheter) followed by a perineural local anesthetic infusion via the remaining catheter (when desired). Subsequent to the local anesthetic administration, instead of removing the catheter as with all previous continuous peripheral nerve block equipment, electric current may be delivered via the same catheter for up to a total of 28 days. This is potentially revolutionary because it would allow an anesthesiologist to deliver (1) a single-injection peripheral nerve block; (2) a continuous peripheral nerve block; and (3) neuromodulation using a single device that can theoretically be placed in the same amount of time required for a single-injection peripheral nerve block. Instead of providing fewer than 24 hours of postoperative analgesia, up to 28 days of pain control could be delivered without disruption of existing practice patterns. ***The ultimate objective of the proposed research study is to prepare for a large, multicenter clinical trial investigating the use of the RELAY device to provide postoperative analgesia.***

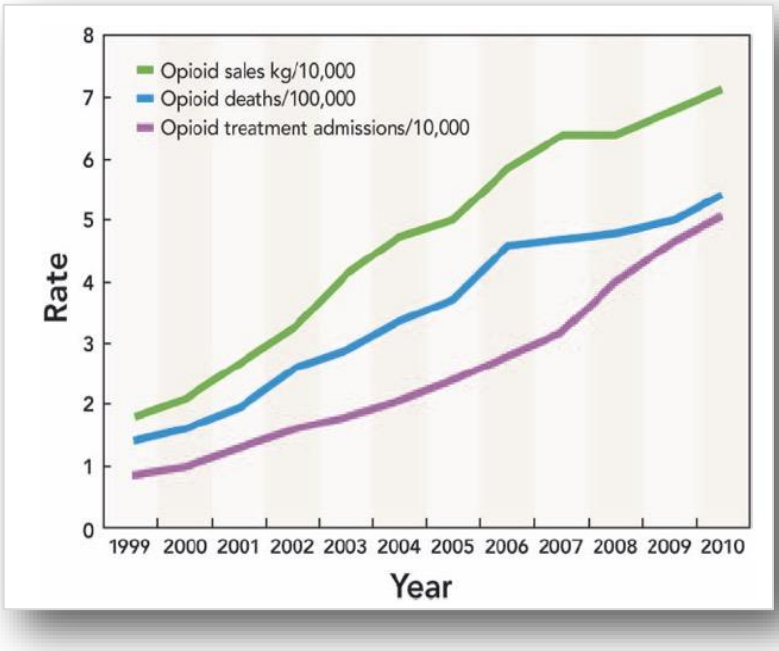
2.2 BACKGROUND

There are tens-of-millions of 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, misuse, addiction, and overdose has multiplied dramatically (**Figure 1**), with the overall economic cost of opioid misuse 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

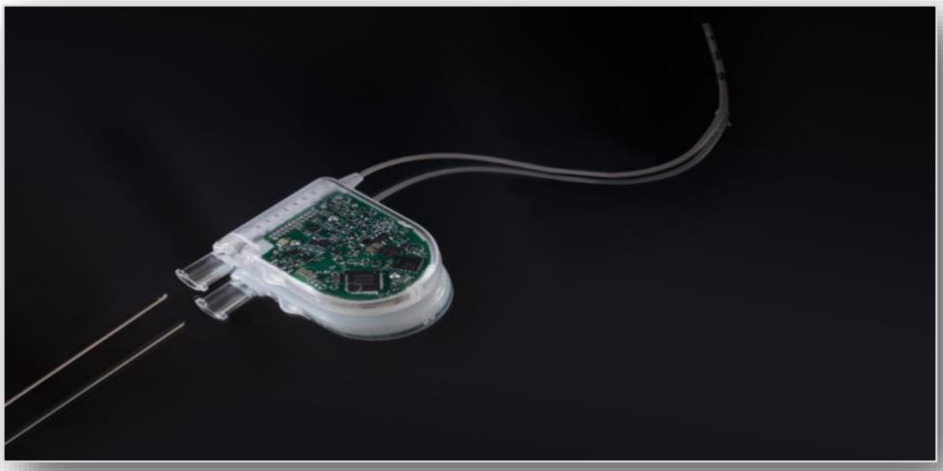


Considering **4-20% of all opioid pills prescribed within the United States are diverted and misused—almost <u>500-million</u> doses annually**—the supply of oral opioids is of great concern. Nearly 80% of misused oral opioids were originally intended for someone else, with most obtained from a friend 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." [Daniulaityte R, Falck R, Carlson RG: Sources of pharmaceutical opioids for non-medical use among young adults. J Psychoactive Drugs 2014; 46: 198-207] Indeed, it has been conclusively demonstrated that both the misuse of opioids and extent of diversion are relative to their prescriptive availability.

Single-injection peripheral nerve blocks have been used for decades to treat postoperative pain but have a duration of action of less than 24 hours. The analgesia may be prolonged with the use of liposomal bupivacaine or a perineural local anesthetic infusion (continuous peripheral nerve block), but these are similarly limited in duration to approximately 72 hours. For many surgical procedures, the duration of pain is measured in weeks and not hours or days. One analgesic alternative—percutaneous peripheral nerve stimulation (PNS)—can improve post-surgical analgesia while concurrently decreasing or obviating opioid requirements without any adverse systemic side effects. However, the only available lead/electrode available to date cleared for treating acute pain within the United States (SPRINT, SPR Therapeutics, Cleveland, Ohio) was developed for chronic pain states and costs over $4,000. Therefore, while this device is being used within clinical research, it is not anticipated to gain widespread use clinically. In addition, this device does not provide the potent analgesia required by patients in the immediate postoperative period, and therefore a single-injection local anesthetic peripheral nerve block is added, requiring two separate procedures and associated equipment.

However, a new device has been developed and is under investigation with an FDA IDE: the RELAY system by Gate Science (Moultonborough, New Hampshire). This device differs from all previous equipment in that it enables a single-injection peripheral nerve block, postoperative perineural local anesthetic infusion, and subsequent neuromodulation, all with a single apparatus. Percutaneous perineural insertion is achieved using standard ultrasound-guidance which places the needle tip adjacent to a peripheral nerve, through which local anesthetic may be injected to induce the peripheral nerve block (duration 8-24 hours). When the needle is withdrawn a perineural catheter remains *in situ* through which a perineural local anesthetic infusion may be delivered (duration up to approximately 72 hours). The device also has an integrated battery, pulse generator, and 3 leads/electrodes that can be activated to provide peripheral nerve stimulation (the device may remain implanted for up to 28 days). Using this combination, optimal postoperative analgesia may be theoretically achieved using 3 different modes of analgesia and all with a single preoperative procedure requiring the skills every anesthesia resident is currently taught (ultrasound-guided regional anesthesia).



Preliminary studies and pilot data.

Gate Science conducted a prospective, open-label, dual-center, randomized, controlled pilot study, to assess preliminary safety, performance, and effectiveness of the RELAY System in participants requiring ankle surgery (bunionectomy, ankle fusion, ankle fracture), knee surgery (total knee replacement), and shoulder surgery (rotator cuff repair, labral repair and capsulorraphy).

A total of 29 participants were enrolled out of the 63 planned. Based on an interim analysis of the study data, it was determined that demonstration of efficacy in this study was unlikely and refinement to the study design and conduct would potentiate the demonstration of clinically relevant efficacy

Overall RELAY was safe and well tolerated (summary table provided in Table 3). Twelve of 19 participants (63.2%) who received RELAY reported at least one adverse event as compared to one of 9 participants (11.1%) in the SOC arm. The disparity in adverse events between RELAY and SOC is largely attributable to placement of the catheter, detailed below. The majority of participants in the RELAY arm experienced mild AEs (9 of 12 participants, 47.4%) with only 2 participants reporting moderate AEs (pain at insertion site) and 1 patient with a severe AE (implant breakage).

The severe AE was coded to implant breakage. As the catheter was being pulled out on Day 28 by the patient per protocol, the catheter broke and the sheared fragment was left embedded in the thigh near the adductor canal insertion site. An ultrasound scan confirmed a portion of catheter remained in sartorius muscle in the leg. *This event resulted in a* secondary surgical intervention (SSI). The catheter fragment was removed by a surgeon under sedation and local anesthesia.

A second subject reported pain at the thigh area which resulted in routine removal of the RELAY device early on Day 13. This event was classified by the Investigator as an SSI, although it does not meet clearly meet the definition of an SSI.

Table 3: Safety Summary

	RELAY (n=19)	**SOC (n=9)**	**Total (n=28)**
At least one Adverse Event	12 (63.2)	1 (11.1)	13 (4.8)
Severity Mild Moderate Severe	 9 (47.4) 2 (10.5) 1 (5.3)	 0 1 (11.1) 0	 9 (32.1) 3 (10.7) 1 (3.6)
Serious Adverse Event	0	0	0
Unexpected Adverse Device Effect	0	0	0
Resulted in SSI	2 (10.5)	0	2 (7.1)

The most common AEs reported by patient who received the RELAY device, regardless of causality are as follows:

- Pain: 6 participants/9 events (6 mild, 3 moderate)
- Weakness: 6 participants/6 events (6 mild)
- Redness/itching/irritation: 4 participants/4 events (4 mild)
- Numbness/tingling: 3 participants/3 events (3 mild)

The disparity in adverse events between RELAY and SOC is largely attributable to placement of the catheter. The adverse events of redness and pain (tenderness) observed at the insertion site are consistent with local inflammatory response to percutaneous devices and are frequently seen with other similar devices such as perineural catheters, and percutaneous intravenous central lines (Jeng et al. Complications of peripheral nerve block. Br J Anaesth, December 2010; 105(1): I97-I1071). The dressing (Tegaderm impregnated with chlorohexidine), applied to the skin to cover and secure the catheter insertion site can also cause redness and irritation. These resolve once the dressings are removed (dos Santos et al. Local Cutaneous Effects Associated with Chlorhexidine Impregnated Gel Dressing in Hematopoietic Stem Cell Transplantation Patients. Open Journal of Nursing, 2018; 8: 115-129.).

These findings are consistent with reports for the approved Sprint device (SPR Therapeutics) which are percutaneously implanted and left in place up to 60 days "the most common adverse event reported in clinical studies was skin irritation due to components being adhered to the skin (which may include inflammation, mild blistering, and/or redness). The majority of the adverse events in clinical studies were resolved with little to no intervention within a few days, and none were classified as serious (*www.sprtherapeutics.com/patients/faq/#:~:text=The%20most%20common%20adverse%20event,after%20lead%20placement%20and%20infection*). These reactions resolved spontaneously with removal of the device. None of the patients in these studies developed infection.

While there was a modest trend favouring RELAY in the primary efficacy measure (AUE, Days 1-7, NRS), the expected efficacy (utilizing the NRS scale) was not achieved. An approximately 50% reduction in opioid use was observed in the RELAY arm.

Significance. The present application proposes applying percutaneous PNS to the most painful **ambulatory** surgical procedures to improve postoperative analgesia and dramatically reduce opioid requirements following local anesthetic resolution. 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 surgical procedures, 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 surgical 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 misused
- The misuse of opioids and extent of diversion are relative to their prescriptive availability
- Illicit opioid use has grown to epidemic proportions

Ultrasound-guided percutaneous PNS has demonstrated extraordinary potential to provide potent postoperative analgesia and concurrently reduce opioid requirements, and is already cleared by the US FDA for use in treating post-surgical pain using a different delivery device. Most importantly—and in contrast to opioids—**neuromodulation has no abuse/addiction potential, produces no adverse systemic side effects, and does not influence cognitive functioning whatsoever.**

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The techniques used in this study have been used to treat pain for decades. However, the specific device we will be using is currently investigational and we will therefore be working under an FDA IDE. The risks listed here are drawn from experience with FDA-cleared devices; and there may be risks that are not yet known (the incidences provided are all estimated for the device under investigation).

1. **Infection** (low risk). The perineural catheters will be inserted under sterile conditions and affixed using liquid adhesive and a sterile occlusive chlorohexidine-impregnated dressing. Phone calls to participants will include questions regarding signs and symptoms of catheter site infection. Should a catheter site become suspicious for infection, the site will be evaluated by a physician investigator. If indicated, the catheter will be removed, the catheter tip cultured, and the subject placed on the appropriate antibiotics. Of note, there are no reported permanent sequelae from a perineural catheter infection in the published literature.
2. **Bleeding** (very low risk). There is the risk of bleeding since the needle and catheter will be inserted through the skin into muscle. If this was to happen, we would hold pressure until the bleeding stopped.
3. **Catheter dislodgement** (low risk). There is a risk of the catheter being accidentally and prematurely dislodged. The RELAY system has small integrated anchors that theoretically decrease dislodgement (removal of the catheter is achieved by simply rotating the catheter which releases the anchors); liquid adhesive will be applied along with a sterile occlusive dressing covering the catheter entry site. Should a catheter be accidentally dislodged, participants have the option of returning to the center to have the catheter replaced as soon as possible. Of note, accidental catheter dislodgement has never been reported to cause injury—just a cessation of the perineural local anesthetic infusion. If it occurs and a participant elects to have the catheter replaced, there may be the inconvenience and same risks as listed above as for the initial catheter insertion.
4. **Pain during catheter and lead implantation** (low risk). Although we use local anesthetic to anesthetize the skin and muscle through which the implanting needle travels, participants may experience discomfort or pain during catheter and lead implantation as well as postoperative neurostimulation. If this occurs, we will administer intravenous fentanyl as is standard practice when administering peripheral nerve blocks.
5. **Pain post-operative** (medium risk). If the pain occurs postoperatively, participants will attempt to achieve pain relief by increasing amplitude of stimulation with the Gate Keeper app. Participants in the training run-in period with a continuous peripheral nerve block, will use their pump's integrated bolus button to administer additional local anesthetic, when needed if pain persists. If pain relief is not achieved and pain remains (NRS ≥4), participants are instructed to take prescribed opioids q4h. *Note: 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).

6. **Nerve injury** (very low risk). The risk of a nerve injury with a local anesthetic-based peripheral nerve block is approximately 1 out of 10,000. No known nerve injuries have occurred with ultrasound-guided percutaneous neuromodulation, although it is theoretically possible.
7. **Lead migration** (very low risk)**.** The lead tip could migrate while the catheter/lead itself remains *in situ*. This could result in a decrease in analgesia.
8. **There is the risk of loss of confidentiality** (low risk). The following procedures will be done to maintain confidentiality: written, paper forms will be kept in a locked medical office and the locked Investigational Pharmacy's files. Computerized records containing personal health information will be stored on password-protected and encrypted computers.

2.3.2 KNOWN POTENTIAL BENEFITS

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

For participants who receive active neuromodulation: Participants 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 constipation. They might also have a lower risk of sleep disturbances, chronic pain, opioid dependence, and mental/physical disability.

Participants 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 constipation. They might also have a lower risk of sleep disturbances, chronic pain, opioid dependence, and mental/physical disability.

Possible benefits to others: Future patients may benefit if it is determined that the RELAY device is feasible and decreases pain, opioid requirements, sleep disturbances, and the incidence of chronic pain. With the opioid epidemic, any decrease in opioid requirements would be a welcome development and could benefit society greatly.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

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 opioids—the standard of care for the past 100 years—that would completely revolutionize postoperative analgesia, as we know it.

The risks of percutaneous neuromodulation are minimal compared with opioids. There have no previous cases of permanent negative sequelae reported in the literature, and we therefore believe that the potential risks of percutaneous neuromodulation are minimal compared to the potential benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess postoperative ***analgesia*** that extends beyond the duration of the local anesthetic interventions to prepare for a subsequent pivotal definitive clinical trial with the RELAY device as compared to sham control.	Difference in the average daily pain intensity for Days 1-7 as measured with the NRS within the BPI between the RELAY device and sham control arms.	Pain negatively influences physical and emotional functioning.
Key Secondary		
To estimate the effect on ***opioid consumption*** of neuromodulation via the RELAY device as compared to sham control	Neuromodulation with the RELAY device will decrease cumulative **opioid consumption** during the first postoperative week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (measured in oxycodone equivalents).	Opioid use has negative individual and society consequences
To estimate the effect on ***physical and emotional functioning*** of neuromodulation via the RELAY device as compared to sham control	The **physical and emotional functioning** of participants will be improved on postoperative Day 3 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (as measured with the BPI Interference Subscale)	Pain negatively influences physical and emotional functioning.
Other Secondary		
To estimate the effect on ***physical and emotional functioning*** of neuromodulation via the RELAY device as compared to sham control	The **physical and emotional functioning** of participants will be improved on postoperative Day 7 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (as measured with the BPI Interference Subscale)	Pain negatively influences physical and emotional functioning.
To estimate the **analgesic effect** of neuromodulation via the RELAY device as compared to sham/placebo for the RELAY device following foot and shoulder surgical procedures at various time points post-treatment	Neuromodulation with the RELAY device will decrease **pain intensity** (as measured by the “average” and “worst” (maximum) daily NRS within the BPI) on Days 1, 2, 3, 4, 7, 8, and 14 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block.	Pain negatively influences physical and emotional functioning.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
To estimate the **analgesic effect** of neuromodulation via the RELAY device as compared to sham/placebo for the RELAY device following foot and shoulder surgical procedures at various time points post-treatment	Neuromodulation with the RELAY device will decrease **pain intensity** (as measured by "current" and "least" daily NRS within the BPI) on Days 3 and 7 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block.	Pain negatively influences physical and emotional functioning.
To estimate the effect on **opioid consumption** of neuromodulation via the RELAY device as compared to sham/placebo for the RELAY device following foot and shoulder surgical procedures at various time points post-treatment	Neuromodulation with the RELAY device will decrease daily **opioid consumption** following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (measured in oxycodone equivalents on Days 1, 2, 3, 4, 7, 8 and 14).	Opioid use has negative individual and society consequences
To estimate the effect on **sleep disturbances** of neuromodulation via the RELAY device as compared to sham/placebo for the RELAY device following foot and shoulder surgical procedures at various time points post-treatment	Neuromodulation with the RELAY device will decrease cumulative **awakenings due to pain** following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (evenings of postoperative Days 1, 2, 3, 4, 7, 8 and 14)	Poor sleep quality is correlated with inferior analgesia and functioning
To evaluate the **masking quality** of the study protocol	The **masking assessment** on Post-op Day 1	Successful masking reduces bias

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-center, sham-controlled study to investigate the efficacy and safety of RELAY use of a device that enables the delivery of both local anesthetic and neuromodulation (peripheral nerve stimulation) to treat postoperative pain.

Following a training run-in period, the randomized single blind sham-controlled part of the study will commence. The purpose of the training run-in period is to ensure that RELAY can be safely placed next to a target nerve, successfully programmed and induce peripheral nerve block and neuromodulation based on the instructions for use. This will ensure familiarity with the device prior to the randomized portion of the study. The training period will consist of up to 20 participants (~ 5 to 10 catheter lead insertions per anesthesiologist) across at least two different surgical procedures.

It is anticipated that during the training run-in phase, the successful deployment of the RELAY system will be achieved 80% or more of the time. If less than 80% is achieved, the study will not proceed to the randomized portion. A brief study report will be submitted to the FDA prior to initiating the randomized portion.

RELAY deployment success will be defined as a successfully placed catheter/lead as evidenced by sensory changes in the distribution of the target nerve with (1) electrical stimulation eliciting paresthesia and (2) inducing a conduction nerve block with injection of local anesthetic injection leading to either decreased or absent sensation to cold with alcohol swab.

The randomized portion will include 40 participants (with up to 10 additional participants to account for drop-outs) randomized (1:1) to the experimental and sham arms, respectively. A futility analysis will be performed once 20 participants have been randomized and data through post-operative Day 7 are available. The following two criteria must be achieved to move forward: 1) RELAY deployment success in the lead/catheter insertion of ≥ 85% in RELAY participants, and 2) a conditional power (Cp) of ≥30% for the primary efficacy endpoint. Of note, a standardized effect size of 0.49 would not meet criteria to continue. There will be no stopping for early efficacy.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Postoperative pain remains undertreated with inadequate analgesic options. Opioids have well-known limitations for both individuals and society; single-injection and continuous peripheral nerve blocks provide intense analgesia but are limited in duration to 24-72 hours; and current neuromodulation options—with a duration measured in weeks and not hours—are prohibitively expensive and require an additional procedure. One possible solution is a device currently under investigation to treat postoperative pain. The RELAY system (Gate Science, Moultonborough, New Hampshire) is comprised of a basic catheter-over-needle device to allow administration of a single-injection of local anesthetic via the needle (or catheter) followed by a perineural local anesthetic infusion via the remaining catheter (when desired). Subsequent to the local anesthetic administration, instead of removing the catheter as with all previous continuous peripheral nerve block equipment, electric current may be delivered via the same catheter for up to a total of 28 days. This is potentially revolutionary because it would allow an anesthesiologist to deliver (1) a single-injection peripheral nerve block; (2) a continuous peripheral nerve block; and (3) neuromodulation using a single device that can theoretically be placed in the same amount of time required for a single-injection peripheral nerve block. Instead of providing fewer than 24 hours of postoperative analgesia, up to 28 days of pain control could be delivered without disruption of existing practice patterns. ***The ultimate objective of the proposed research study is to prepare for a large, multicenter clinical trial investigating the use of the RELAY device to provide postoperative analgesia.***

4.3 JUSTIFICATION FOR DOSE

Regarding the local anesthetics, we are using standard volumes and concentration of local anesthetics currently used at our institution. We do not want to change our standard of care for the local anesthetic-based peripheral nerve blocks.

Regarding the electrical stimulation, the pulse generator of the RELAY has a frequency between 1-250 Hz, a pulse duration of 1-200 µs, and a current of 0.001-10 mA (1-10,000 µA). If the same pattern holds for the RELAY device as for previously tested peripheral nerve stimulators, we will maximize frequency, minimize pulse duration, and have participants adjust the amplitude, as needed. Participants will use their smartphone to download an app that allows them to increase or decrease the amplitude using a Bluetooth connection with the pulse generator. Participants can only adjust the amplitude and not the other parameters.

4.4 END OF STUDY DEFINITION

The end of the study is defined as completion of the last follow up data collection time point (14 days) of the final enrolled participant.

5 STUDY POPULATION

We will be enrolling adult participants (at least 18 years of age) undergoing a rotator cuff repair, total shoulder arthroplasty, hallux valgus correction, or ankle arthroplasty/arthrodesis. Up to 20 participants will be enrolled to the training run-in period. An additional 40 participants are anticipated for the randomized portion of this study. However, to account for dropouts, will are requesting an additional 10 participants. This will total up to 70 participants overall.

5.1 INCLUSION CRITERIA

1. Adult participants of at least 18 years of age
2. Undergoing a rotator cuff repair, total shoulder arthroplasty, hallux valgus correction or ankle arthroplasty/arthrodesis
3. Planned single-injection peripheral nerve block(s)
4. An Android or Apple smartphone able to download the Gate Keeper controller app

5.2 EXCLUSION CRITERIA

1. Chronic opioid or tramadol use (daily within prior 2 weeks and duration > 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 of infection
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
7. Allergy to skin-contact materials (occlusive dressings, bandages, tape etc.)
8. Incarceration
9. Pregnancy
10. Moderate pain (NRS > 3) in an anatomic location other than the surgical site
11. Anxiety disorder
12. History of substance misuse
13. Inability to communicate with the investigators
14. Inability to contact the investigators during the treatment period, and vice versa (e.g., lack of telephone access)
15. Allergy to amide local anesthetics
16. Morbid obesity (body mass index > 40 kg/m^2)

5.3 LIFESTYLE CONSIDERATIONS

Not Applicable.

5.4 SCREEN FAILURES

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

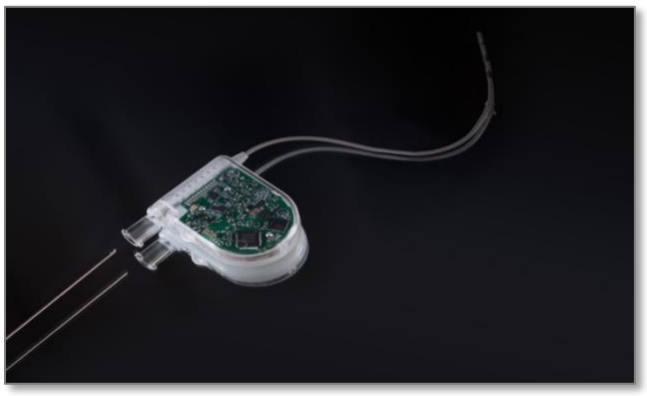
6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

For individuals of childbearing potential, a sample of urine will be collected before any study interventions to confirm a non-pregnant state (this is standard procedure for all surgical patients) [**standard of care**].

The RELAY device combines a catheter-over-needle to permit ultrasound-guided percutaneous insertion with the tip adjacent to a peripheral nerve or plexus, followed by needle removal which leaves the catheter in situ to deliver a bolus of local anesthetic (if desired) and subsequent perineural local anesthetic infusion (if desired). The catheter also has 3 integrated electrodes to enable neuromodulation using the integrated pulse generator and battery (figure below).



Participants will have standard external monitors placed and oxygen delivered by facemask or nasal cannula [**standard of care**]. The peripheral nerve block site(s) will be cleansed with chlorhexidine gluconate and isopropyl alcohol [**standard of care**]. Intravenous sedation/analgesia with midazolam and/or fentanyl will be titrated for patient comfort as is standard for peripheral nerve block administration [**standard of care**]. ***The nerves treated will include the sciatic proximal to the popliteal crease for foot surgery and the brachial plexus for shoulder surgery*** [**standard of care**]. The target nerve(s) will be visualized with ultrasound using a transverse cross-sectional (short axis) view and a skin wheal of local anesthetic will be raised inferior to the transducer to anesthetize the skin and then the track towards the target [**standard of care**].

Treatment group allocation (randomization).

All participants in the training run-in period will receive active neuromodulation [**research specific**].

Participants in the randomized portion of the study will be randomized and allocated to one of two possible treatments groups [**research specific**]:

- ***Neuromodulation***
- ***Sham (Control)***

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

Randomization [***all* research specific**] will be stratified by anatomic location (shoulder and foot/ankle surgery) in a 1:1 ratio and in blocks of 2. Computer-generated randomization lists will be created by the UC San Diego Investigational Drug Service and the allocation provided to the investigators *via* sequential, opaque envelopes. Pulse generators are available that are capable of either (1) passing electrical current; or (2) not passing electrical current. Importantly, these 2 modes (active and sham) are indistinguishable in appearance, and therefore investigators, participants, and all clinical staff will be masked to treatment group assignment, with the only exception being the unmasked individuals who insert the RELAY and program the stimulator.

The RELAY system with the integrated needle will be inserted adjacent to the target nerve with an in-plane approach [**same as standard-of-care**]. Dextrose 5% in water (1-20 mL) will be injected via the needle to open a space around the target nerve(s) [**research specific**], the catheter advanced [**same as standard-of-care**], and the needle subsequently withdrawn [**same as standard-of-care**].

Electrical current will be introduced with increasing intensity via each of the anode electrodes to optimize participant's perceived stimulation (control provided by the Gate Keeper app from an investigator's phone or tablet). Accurate lead placement will be confirmed with subject reports of comfortable sensations over the surgical site without eliciting muscle contractions. The minimum threshold and maximum comfortable amplitudes will be determined along with the optimal frequency, pulse duration, and anode/cathode. Starting from the lowest possible current we increase the current until the participant states that they feel a "buzzing" sensation (some describe it as a "comfortable massage"). That is the minimal sensed current. We then continue increasing with the instructions to let us know when it starts to be less comfortable—and to stop us before it hurts. That is the maximum comfortable current. The stimulator will be then set to deliver the minimum threshold amplitude and turned off for surgery. **Sham treatment group** [***all* research specific**]**.** For participants receiving **sham** treatment, electric current will not reach the anodes, but the investigators will connect to the RELAY to the mobile phone or tablet just as with the active group and set the parameters as follows: anode (distal), cathode (proximal), frequency (100 Hz), pulse duration (100 μs), and amplitude (5 mA).

Local anesthetic for active and sham groups. Local anesthetic (10 mL of lidocaine 2% with epinephrine) will be injected with negative aspiration every 3 mL and resulting sensory block confirmed to ensure accurate catheter tip placement [**research specific**]. Following block confirmation (sensory deficits in the expected nerve distributions), the RELAY will be affixed with both surgical adhesive (2-Octyl 2-cyanoacrylate) at the entry site and a chlorohexidine-impregnated occlusive dressing [**research specific**]. Subsequently, 10 mL of bupivacaine 0.5% with epinephrine will be injected negative aspiration every 3 mL along with a supplemental single-injection saphenous nerve block for foot/ankle surgery [**standard of care**].

Intraoperatively, surgeons will be permitted to infiltrate the surgical area with long-acting local anesthetic as their common practice dictates [**standard of care**].

Postoperatively, the stimulators will be connected to participants' phones and turned on [**research specific**].

For the training run-in period, if a patient's surgeon requests a postoperative continuous peripheral nerve block, a ropivacaine 0.2% infusion will be provided per standard UC San Diego protocol [**standard of care**].

After 7 days, participants in both the active and sham groups, themselves or their caretaker will remove the occlusive dressing and withdraw the catheter (and integrated electrodes) with gentle traction and rotation at home [**research specific**]. The devices are single-use and disposable [**research specific**].

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

6.1.2 DOSING AND ADMINISTRATION

The pulse generator of the RELAY has a frequency between 1-250 Hz, a pulse duration of 1-200 µs, and a current of 0.001-10 mA (1-10,000 µA). We will maximize frequency, minimize pulse duration, and have participants adjust the amplitude, as needed. Administration is described above in 6.1.1.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The RELAY device will be shipped to the clinical trial site by Gate Science. Accountability records will be maintained at the site.

Any investigational medical device that is defective will be sent back to Gate Science, and the investigational medical device will be resupplied to replace the defective. When the device is explanted, it will be discarded. Any remaining device at the site at the end of the study will be returned to Gate Science.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

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

6.2.3 PRODUCT STORAGE AND STABILITY

The RELAY system will be stored in the Principal Investigator's or Program Manager's locked office or the locked anesthesia workroom.

The expiration of RELAY is based on date of manufacture and is provided to the clinical trial site and will be monitored accordingly by the Sponsor.

6.2.4 PREPARATION

The RELAY devices do not need "preparation".

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomized portion of the study will utilize a randomized, observer- and participant-masked, sham/placebo-controlled protocol. Randomization will be stratified by surgical procedure (shoulder and foot/ankle surgery) in a 1:1 ratio and in blocks of 2. Computer-generated randomization lists will be created by the UC San Diego Investigational Drug Service and the allocation provided to the investigators in sequential, opaque envelopes. A masking assessment question will be queried on postoperative Day 1.

6.4 STUDY INTERVENTION COMPLIANCE

Not applicable.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE MEDICINE

As inpatients, our current standard analgesic protocol will be followed: acetaminophen 975-1000 mg po QID, oxycodone 5-10 mg po q4 h prn moderate pain (NRS 4-7), and morphine 1-2 mg IV prn severe pain (NRS>7). Prior to discharge, participants will all be provided with a prescription for oxycodone (5 mg tablets) by their surgeon, as dictated by our current standard of care. If pain occurs postoperatively, participants will attempt to achieve pain relief by increasing amplitude of stimulation with the Gate Keeper app. Participants in the training run-in period with a continuous peripheral nerve block, will use their pump's integrated bolus button to administer additional local anesthetic, when needed if pain persists. If pain relief is not achieved and pain remains (NRS ≥4), participants are instructed to take prescribed opioids q4h.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Catheter/lead implantation will be discontinued if the participant requests during the procedure. The catheter/lead may be removed at any time of the participant's choosing within the first week after surgery.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

7.2.1 DISCONTINUATION CRITERIA

1. Participants may withdraw voluntarily from participation in the study at any time and for any reason.
2. Participants may be withdrawn on the basis of the Investigator's clinical judgment, protocol deviation or loss to follow-up.
3. This study may be terminated at the discretion of any regulatory agency for reasons including safety and/or efficacy.
4. The Primary Investigator may elect to discontinue or stop the study for any reason including safety.
5. When a participant withdraws or is withdrawn before completing the study, the date and reason for withdrawal are to be documented in the CRF.
6. In the event that a patient is withdrawn prematurely due to an AE or serious AE, the AE or serious AE will be followed until it resolves or stabilizes, or until it is judged by the Principal Investigator to be no longer clinically significant.

7.3 LOST TO FOLLOW-UP

Study participants may miss data collection phone calls—it is common even though the investigators attempt multiple contacts with participants at specified times—but this study will not consider any patient "lost to follow-up". We may not be able to collect all data for all participants at all study time points; but we will continue to attempt to contact participants until 14 days have passed for that participant (the duration of study participation) or the participant requests study withdrawal (in which case it is a withdrawal and not "lost to follow-up").

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

Outcome measurements. We have selected outcome measures that have established reliability and validity, with minimal inter-rater discordance, and are recommended for pain clinical trials by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement. The primary outcome measure will be the median "average" daily ***pain intensity*** for Days 1-7 as measured with the NRS within the BPI. The primary analysis will compare the two treatments (inter-subject comparisons) in which half of the participants will receive active neuromodulation and the other half a sham/placebo neuromodulation. Endpoints will be evaluated on postoperative Days 1, 2, 3, 4, 7, 8, and 14. In addition, participants will receive a phone call the evening of postoperative Day 0 (the day of surgery) to answer any questions they may have about the stimulator or study protocol.

Each time the questionnaire is applied, participants will be instructed to respond for the previous 24 hours. The exception will be on Day 1 because at these time points, the interest is in participants' experiences subsequent to discharge from the recovery room. During this day only, participants will be instructed to respond for the period of time since they were discharged from the recovery room.

We will record basic anthropomorphic characteristics (e.g., age, physiological sex, height, and weight), intervention characteristics (e.g., pulse generator parameters, catheter insertion duration, minimum/maximum comfortable amplitude), surgical characteristics (e.g., surgical duration) and protocol deviations / adverse events.

All data collection following the day of the intervention (Day 0) will be collected by telephone from the University of California San Diego by the investigators, Program Manager, and/or research coordinators specifically trained in these instruments' application, minimizing inter-rater discordance and standardizing responses across all enrolling centers. Observers masked to treatment group assignment will perform all postoperative assessments. Each data collection phone call will require approximately 5 minutes.

In addition to the outcomes described below, we will record awakenings due to pain at each data collection phone call, as well as any sensory deficits for participants with continuous peripheral nerve blocks, and patient-controlled changes to the neuromodulation amplitude. On postoperative day 1 we will query participants on whether they believe they are receiving active or sham stimulation (a masking assessment).

> ***Hypothesis 1:*** Neuromodulation with the RELAY device will decrease ***pain intensity*** for Days 1-7 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (as measured with the NRS within the BPI).

Current/present, worst, least, and average `surgical pain will be assessed using the NRS as part of the BPI (short form), with the "average" pain scores collected on postoperative days 1, 2, 3, 4 and 7 designated as the primary endpoint. The NRS is a highly-sensitive measure of pain intensity with numbers ranging from 0 to 10, zero equivalent to no pain and 10 equivalent to the worst imaginable pain. The NRS has been demonstrated to be a valid and reliable measure in multiple pain states and following analgesic interventions. In addition, NRS scores correlate well with other measures of pain intensity, and demonstrate high test-retest reliability in chronic nociceptive and neuropathic pain states. These NRS characteristics led to recent IMMPACT consensus recommendations for use of the 10-point NRS of pain intensity for pain trials.

Hypothesis 2: Neuromodulation with the RELAY device will decrease ***opioid consumption*** within the week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (measured in oxycodone equivalents)***,*** as measured both with daily and cumulative opioid consumption within the first postoperative week).

Opioid analgesic consumption will be recorded at all time points (Table 2), with the secondary outcome measure of greatest importance being the cumulative opioid dose in oral oxycodone equivalents for the first 7 postoperative days following recovery room discharge. The two treatment groups' daily opioid consumption will also be compared at all timepoints, including Day 14.

Hypothesis 3: Physical and emotional functioning as measured with the Interference Subscale of the BPI. Neuromodulation with the RELAY device will decrease pain's ***interference*** in physical and emotional ***functioning*** within the week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block.

It is well-recognized that, "pain is a complex, multidimensional, sensory, and emotional experience that is individually perceived and described in many different ways." This observation has led to consensus recommendations that "multiple core domains and related measures be considered in pain treatment trials," that "tap into a wider experience of pain over time and its impact on functioning and quality of life." Therefore, the proposed trial will include the BPI, an instrument that includes—in addition to pain intensity scales—seven measures evaluating the pain's interference with physical and emotional functioning, such as sleep, relations with others, and enjoyment of life. It is this 7-question Interference Scale that will be used specifically for Hypothesis 3. The BPI has been used and validated in countless clinical pain-related studies. This instrument is associated with minimal subject burden and is easily interpreted by participants of all ages and education levels. It has high test-retest reliability and correlates well with much longer questionnaires, including the McGill measures and EuroQol. The secondary outcome measures of greatest interest after the cumulative opioid consumption will be the Interference Scale (0-70) recorded on Day 3.

8.2 SAFETY AND OTHER ASSESSMENTS

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

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

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

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

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

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

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

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

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

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

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

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

8.3.3.3 EXPECTEDNESS

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

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

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

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

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

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

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

Precautions and responses to possible specific adverse events:

Infection: The perineural catheters will be inserted under sterile conditions and affixed using liquid adhesive and a sterile occlusive chlorohexidine-impregnated dressing. Phone calls to participants will include questions regarding signs and symptoms of catheter site infection. Should a catheter site become suspicious for infection, the site will be evaluated by a physician investigator. If indicated, the

catheter will be removed, the catheter tip cultured, and the subject placed on the appropriate antibiotics.

Bleeding: There is the risk of bleeding since the needle and catheter will be inserted through the skin into muscle. If this was to happen, we would hold pressure until the bleeding stopped.

Catheter dislodgement. There is a risk of the catheter being accidentally and prematurely dislodged. The RELAY has small integrated anchors that theoretically decrease dislodgement (removal of the catheter is achieved by simply rotating the catheter which releases the anchors); liquid adhesive will be applied; a sterile occlusive dressing will cover the catheter entry site. Should a catheter be accidentally dislodged, participants have the option of returning to the center to have the catheter replaced as soon as possible. Of note, accidental catheter dislodgement has never been reported to cause injury—just a cessation of the perineural local anesthetic infusion.

Lead migration. The lead tip could migrate while the catheter/lead itself remains *in situ*. This could result in a decrease in analgesia. Should a catheter/lead migrate, participants have the option of returning to the center to have the catheter replaced as soon as possible.

Pain. Although we use local anesthetic to anesthetize the skin and muscle through which the implanting needle travels, participants may experience discomfort or pain during catheter and lead implantation as well as postoperative neurostimulation. If this occurs, we will administer intravenous fentanyl as is standard practice when administering peripheral nerve blocks. If the pain occurs postoperatively, participants will attempt to achieve pain relief by increasing amplitude of stimulation with the Gate Keeper app. participants in the training run-in period with a continuous peripheral nerve block, will use their pump's integrated bolus button to administer additional local anesthetic when needed if pain persists. If pain relief is not achieved and pain remains (NRS ≥4), participants are instructed to take prescribed opioids q4h. Note: Not all surgeons at UC San Diego use continuous peripheral nerve blocks; and those who do use them do so for some participants, but not others (depending on various surgical factors or simply their opinion of the technique).

Nerve injury (very low risk). The risk of a nerve injury with a local anesthetic-based peripheral nerve block is approximately 1 out of 10,000. No known nerve injuries have occurred with ultrasound-guided percutaneous neuromodulation, although it is theoretically possible. If a nerve injury was to occur, the participant would be referred to neurology for evaluation and management. The investigators would follow.

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

8.3.5 ADVERSE EVENT REPORTING

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

8.3.6 SERIOUS ADVERSE EVENT REPORTING

SAEs must be reported within 24 hours of discovery to Gate Science via a completed SAE form. The study investigator shall submit all SAEs to the UCSD Office of IRB Administration as soon as possible, but no later than 10 working days after the investigator first learns of the effect.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

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

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

Conception following the surgical procedure is not considered an AE for this study: there is no prohibition against pregnancy with peripheral nerve stimulation (it is far preferred over systemic opioid consumption).

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

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

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

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report UPs to Gate Science and to UCSD Office of IRB Administration. The UP report will include the following information:

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

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 days of the investigator becoming aware of the event.

- Any other UP will be reported to the IRB within 30 days of the investigator becoming aware of the problem.
- All unanticipated events and adverse events will be reported to the supervising IRB (University of California San Diego).

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Hypothesis 1: Neuromodulation with the RELAY device will decrease ***average pain intensity*** for Days 1-7 following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (as measured with the NRS within the BPI).

Hypothesis 2: Neuromodulation with the RELAY device will decrease ***opioid consumption*** within the week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block (measured in oxycodone equivalents), as measured both with daily and cumulative opioid consumption within the first postoperative week).

Hypothesis 3: Physical and emotional functioning as measured with the Interference Subscale of the BPI. Neuromodulation with the RELAY device will decrease pain's ***interference*** in physical and emotional ***functioning*** within the week following foot and shoulder surgery currently treated with a single-injection peripheral nerve block.

9.2 SAMPLE SIZE DETERMINATION

The sample size estimation is centered around the hypothesis that neuromodulation lowers the severity of pain the week after surgery. To this end, the primary outcome measure is the median "average" daily pain intensity for Days 1-7 as measured with the NRS within the BPI. This outcome measure was used by the authors previously for a similar study treating the same patient population with a different percutaneous peripheral nerve stimulation pulse generator and lead, and we therefore will use the resulting mean (SD) from each treatment group to power the present pilot study [Ilfeld et al. Anesthesiology 2021; 135: 95-110]. Specifically, the treated and sham groups reported a mean (SD) of 1.1 (1.1) and 3.1 (1.7), respectively. Assuming a standard deviation of 2.05, a sample size of 20 participants per group provides 85.2% power to detect a group difference of 2 points. With an additional 10 participants allowed to replace drop-outs in the randomized portion, a total of up to 70 participants may be enrolled in this study combining the run-in and randomized stages.

9.3 POPULATIONS FOR ANALYSES

A total of 40 individuals are anticipated for the randomized portion of the trial; however, an additional 10 may be enrolled to account for dropouts.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Baseline characteristics of the randomized groups will be summarized with means, standard deviations, and quartiles. Balance between groups will be assessed following the approach described by Schober (2018). Specifically, standardized differences will be calculated using Cohen's d whereby the difference in means or proportions is divided by the pooled standard deviation estimates. Any key variables (age, sex, height, weight, BMI, and surgical procedure) with an absolute standardized difference greater than $1.96\times\sqrt{2/n}$ = 0.716, where $n = 15$ is the target sample size per group (Austin (2009)), will be noted and included in a sensitivity analysis with a generalized linear model (e.g. linear regression for pain severity NRS or logistic regression for incidence rates) to obtain an estimate of the treatment effect adjusted for the imbalanced covariate(s). If key model assumptions are violated (i.e. homoscedasticity or Gaussian distribution for linear models), data transformations and/or alternative generalized linear models will be applied as appropriate. Missing data is expected to be negligible. In the event of unexpected missing data, multiple imputation by chained equations (Stef van Buuren, Karin Groothuis-Oudshoorn (2011). mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software, 45(3), 1-67) will be applied to obtain estimates of treatment effects under the assumption of missing at random. The imputation model will exhaustively consider all measured baseline covariates and longitudinal observations to maximize the likelihood that the missing at random assumption is met.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary analytic approach will be an unadjusted two-sample Mann-Whitney U test of the median value of each participant's average daily NRS for Days 1, 2, 3, 4, and 7 (data is not collected on Days 5 and 6). If any key variables are imbalanced at baseline, a linear regression model, or appropriate generalized linear model, adjusting for those variables will be applied. The p-value and 95% confidence interval associated with the estimated group difference in average daily NRS will be provided. P<0.05 will be considered statistically significant for the primary outcomes.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Continuous endpoints will be analyzed with the same approach as the primary endpoint. Binary endpoints will be analyzed with Fisher's Exact test for two proportions, or logistic regression in the event of imbalance on key baseline variables. Ordinal endpoints will be analyzed with the Armitage trend test, or cumulative link regression model as warranted. We will test key secondary outcomes using a serial gatekeeping procedure. Nominal 95% confidence intervals will be provided for secondary analyses.

Study-wide Type I error control. We will use a serial gatekeeping procedure to control the study-wide type I error at 0.05 [Mascha EJ, Turan A: Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. Anesth Analg 2012; 114: 1304-17]. For this procedure we therefore have prioritized (*a priori*) the study outcomes (**Table below**). Analysis will proceed in that order, and testing will proceed through each "gate" to the next set if and only if the outcome in the current set reaches significance. The significance level for each set will be 0.05 times a cumulative penalty for non-significant results in previous sets (i.e., a "rejection gain factor" equal to the cumulative product of the proportion of significant tests across the preceding sets). We will use the corresponding 2-tailed alpha level of 0.05 for the gatekeeping, as all sets involve 2-tailed tests. Treatment effects will also be assessed at individual time points regardless of preceding gatekeeping results, and no other adjustments will be made for testing multiplicity.

Serial gatekeeping procedure

Sets	Time frame	Required to pass to next set

1: Pain intensity (median of 5 daily "average" NRS)	1st week	Significance on this outcome
2: Cumulative opioid use (oxycodone equivalents)	1st week	Significance on this outcome
3: BPI interference subscale	Postop Day 3	Significance on this outcome
4: Pain intensity (median of 5 daily "worst" NRS)	1st week	Significance on this outcome
5: BPI interference subscale	Postop Day 7	Significance on this outcome
6: Cumulative awakenings due to pain	1st week	Significance on this outcome
7: Pain intensity ("average" NRS)	Postop Day 7	Significance on this outcome
8: Pain intensity ("worst" NRS)	Postop Day 7	Significance on this outcome
9: Opioid use (oxycodone equivalents)	Postop Day 7	Significance on this outcome
10: Awakenings due to pain	Postop Day 7	Significance on this outcome
11: Opioid use (oxycodone equivalents each day)	Postop Days 1, 2, 3, 4, 8, 14	Significance on this outcome
12: Pain intensity (each daily "average" NRS)	Postop Days 1, 2, 3, 4, 8, 14	Significance on this outcome
13: Pain intensity (each daily "worst" NRS)	Postop Days 1, 2, 3, 4, 8, 14	Not applicable

9.4.4 SAFETY ANALYSES

Device-related Adverse Events. The investigators will record all device-related adverse events. These complications cannot be "ranked", but rather the two groups will be compared descriptively on each of these possible complications.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

As described above, balance on baseline covariates will be assessed using absolute standardized difference (ASD). Variables considered imbalanced will be adjusted for in the statistical analyses. Analyses will be carried out using modified intention-to-treat i.e., participants who received any study treatment will be analyzed according to the group to which they were randomized.

9.4.6 PLANNED INTERIM ANALYSES

A futility analysis will be performed once 20 participants have been randomized and data through post-operative Day 7 are available. The following two criteria must be achieved to move forward: 1) RELAY deployment success in the lead/catheter insertion of ≥ 85% in RELAY participants, and 2) a conditional power (Cp) of ≥30% for the primary efficacy endpoint. Of note, a standardized effect size of 0.49 would not meet criteria to continue. There will be no stopping for early efficacy.

9.4.7 SUB-GROUP ANALYSES

Descriptive analyses will be performed by surgery type (shoulder or ankle).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

Enrollment. Potential study participants will be identified from the surgical schedule:

Candidates who meet inclusion and exclusion criteria and desire study enrollment will be scheduled to arrive the day of surgery 30 to 60 minutes earlier than normal to allow for written informed consent, baseline information collection, and additional time for study procedures. Written informed consent will be attained prior to any measurements or procedures prior to surgery. When participants present for surgery, an investigator, Program Manager, or research coordinator will provide and attain written informed consent. This will occur in private patient care areas, so that participants may feel comfortable asking questions.

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

This study protocol has follow-up data-collection telephone calls a maximum of 14 days following the initial study treatment, so repeated informed consent following the initial consent is unnecessary, as opposed to multi-year, longer-term clinical trials. Surrogate consent will not be accepted; therefore, if human participants cannot provide consent on their own, they will not be offered study enrollment. Consent by an individual's Legally Authorized Representative is unacceptable for study enrollment.

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

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

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

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

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

3. This clinical trial could not be practicably carried out without the waiver because many relatively healthy surgical patients are not seen in preop clinic; or they are seen just 1-2 days prior to their date of surgery. The investigators will need to know in advance which patients would like to participate in order to have an investigator and research coordinator present on the day of surgery. In addition, we need to bring participants to the surgical center 30 minutes earlier than regularly scheduled in order to provide written, informed consent, record baseline measurements, and leave extra time for the study intervention.

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

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

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

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

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

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

All case report forms (data capture forms, or "CRFs") will be identified by only the randomization number and first and last initials of the participants' names (as a check for the randomization numbers). Therefore, any protected health information will be separated from identifiers. The connection between participant identifiers and the randomization numbers will be accessible solely by the Principal Investigator and Program Manager (for follow-up data collection purposes). Therefore, no case report form will be tied to an identifiable individual on the forms themselves, ensuring patient confidentiality should a form be inappropriately accessed. All case report forms will be retained in the locked offices of the Principal Investigator and/or Program Manager. These hard copies will not be mailed or otherwise transferred and will remain available to audit for a minimum of 7 years. Data will be entered into an Excel spreadsheet kept on a password-protected and encrypted computer and retained by the Principal Investigator for at least 7 years. The IRB is eligible to review study records at any time.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

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

10.1.5 KEY ROLES AND STUDY GOVERNANCE

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

10.1.6 SAFETY OVERSIGHT

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

In addition, Gate Science will appoint a qualified physician as the Independent Medical Monitor (IMM) to oversee all medical monitoring issues and provide safety oversight. The IMM will evaluate the available information during the course of the trial and advise about the continuing safety of the trial to ensure the wellbeing of the study participants

10.1.7 CLINICAL MONITORING

This study will be monitored in accordance with the Clinical Monitoring Plan. The purpose of monitoring is to ensure that:

- The rights and well-being of human subjects are protected;
- The data is accurate, complete and verified from source documents; and

- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The Site Monitor is the liaison between Gate Science and the site and will conduct on-site and remote site visits. The Site Monitor will ensure:

- Investigator has sufficient staff and facilities to conduct the study safely and effectively;
- Investigator has adequate qualifications and resources throughout the study
- Investigator and staff are appropriately trained to properly conduct the study.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

10.1.8.2 STUDY RECORDS RETENTION

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

10.1.9 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

It is the responsibility of the study investigator to use continuous vigilance to identify all deviations and report appropriate deviations (such as those related to an SAE) within 10 working days. All deviations must be addressed in study source documents and ultimately reported to the UCSD Office of IRB Administration.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 ALTERNATIVES TO STUDY PARTICIPATION

Potential study participants may simply decline enrollment.

10.2.2 EXPENSE TO PARTICIPANT

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

10.2.3 COMPENSATION FOR PARTICIPATION

There is no financial compensation for participation.

10.2.4 MANAGEMENT OF ADVERSE EVENTS

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

10.2.5 PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Principal Investigator, Brian M. Ilfeld, MD, MS, is a board-certified anesthesiologist with fellowship training in and 23 post-training years' experience with regional anesthesia, acute pain medicine, and clinical investigation. Dr. Ilfeld holds a license to practice medicine in California. Dr. Ilfeld has medical privileges at the UC Medical Centers. Dr. Ilfeld, or another investigator, will follow all participants following their treatment. Dr. Ilfeld will be responsible for the overall management of this study.

Co-investigators John Finneran, MD, and Engy Said, MD, are board-certified anesthesiologists with experience with regional anesthesia and acute pain medicine. All hold a license to practice medicine in California and medical privileges at the UC Medical Centers. All will help consent participants, perform a history and physical exam, perform the treatment on participants, and will follow participants following their treatment.

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

10.2.6 FUNDING SUPPORT FOR THIS STUDY

There is no extramural funding available for this trial, although the investigators will pursue such funding. However, the manufacturer will be donating the RELAY devices. Department funding will be used in the interim or if no extramural funding is awarded. Please contact Kimberly Giles, grants specialist, at kgiles@health.ucsd.edu for information regarding Departmental funding.

10.3 ABBREVIATIONS

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

10.4 PROTOCOL AMENDMENT HISTORY

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

Version	Date	Description of Change	Brief Rationale
1.5	22 Jan 2025	Funding information is revised to "Gate Science, the study sponsor is paying UC San Diego to conduct this research study."	To clarify funding information.

11 REFERENCES

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12 APPENDIX