Official Title:
The SNAP Trial: SPRINT® peripheral nerve stimulation for the treatment of Neuropathic post-Amputation Pain in a randomized, double-blinded, placebo-controlled, multicenter trial

NCT#: 03783689

Date: 15 January 2021

Information contained in the attached protocol is accurate as of the amendment date above.

The SNAP Trial: SPRINT® peripheral nerve stimulation for the treatment of Neuropathic post-Amputation Pain in a randomized, double-blinded, placebo-controlled, multicenter trial

Sponsor: SPR Therapeutics, Inc.
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Protocol: [redacted]

Amendment Date(s): [redacted]
January 15, 2021

FDA Clearance for SPRINT® PNS System: K170902. K181422.

CONFIDENTIAL INFORMATION
This protocol contains confidential information for use by the Investigator and his designated representatives participating in this clinical study. It should be held confidential and maintained in a secure location. Do not copy or distribute without permission.

Table of Contents

1.0 Protocol Synopsis

Title	The SNAP Trial: SPRINT® peripheral nerve stimulation for the treatment of Neuropathic post-Amputation Pain in a randomized, double-blinded, placebo-controlled, multicenter trial
Test Device (510(k) Cleared)	The SPRINT Peripheral Nerve Stimulation (PNS) System
Study Design	Prospective Randomized, Double-Blinded, Placebo-Controlled, Multicenter Study to collect post-market data on the safety and effectiveness of the treatment.
Study Objective	The study objective is to gather post-market data regarding the safety and effectiveness of the PNS therapy for the treatment of neuropathic pain following amputation. The study will determine if the treatment-specific effect of the treatment is significant and different than the placebo effect.
Study Plan	**Amputees must have an average pain score of [redacted] to qualify** Individuals with lower extremity amputation reporting neuropathic pain in the residual limb and/or phantom limb rated ≥ [redacted] on an 11-point numerical rating scale on the Brief Pain Inventory Short Form (BPI-SF Question #5) will be considered for enrollment into the study. After informed consent is obtained, potential subjects will be evaluated for general eligibility. The individuals who satisfy the preliminary criteria will be asked to complete a 7-day baseline diary to record their daily "average pain" intensity (Question #5 on the BPI-SF) for each region of post-amputation pain (i.e., both residual limb pain and phantom limb pain) for the amputated limb. Individuals must report in either the residual limb or phantom limb an average pain intensity of ≥ [redacted] averaged across the 7-day diary to qualify for lead placement. Individuals only need to report a 7-day average pain intensity ≥ [redacted] in at least one region to qualify. **Percutaneous leads will be placed in the upper leg to stimulate the [redacted] nerves** Qualifying subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control). In all subjects, leads will be placed [redacted] All subjects will be instructed to use the SPRINT Stimulator(s) [redacted]. In Group #1, the system will deliver electrical stimulation [redacted] while in Group #2, the system will deliver sham (placebo) stimulation [redacted] After lead removal, Group #1 subjects will be followed for 12 months from the start of treatment (SOT). **Group #2 will be given the option of crossing over to the PNS treatment** Following the completion of a follow-up visit [redacted] Group #2 subjects will be given the option of crossing over to receive the PNS treatment. If subjects do not choose

to receive stimulation, they will be discharged from the study. If subjects choose to receive stimulation, leads will again be placed [redacted], and the system will deliver electrical stimulation [redacted] After lead removal, the subjects will be followed for 12 months from the start of the crossover stimulation treatment.

The schedule of study visits and assessments is identical [redacted] with scheduled clinic visits at baseline, [redacted] Subjects will additionally receive scheduled telephone calls [redacted]

Daily medications affecting pain will be permitted at levels established during baseline.

All subjects will be permitted to continue use of all baseline medications affecting pain throughout the study; [redacted] To be eligible for lead placement, individuals cannot have added any new medications affecting pain, including as-needed (PRN) medications, within the 4 weeks prior to initiating the baseline diary (based upon the subject-reported medication history). Consistent with clinical practice for clinical trials, subjects will be permitted to use additional over-the-counter (OTC) supplemental medications throughout the study for breakthrough residual limb pain, phantom limb pain, or other pain (e.g., headache, backache, toothache), subject to the limitations and maximum daily dosages defined in the protocol.

Each site will have a blinded evaluator in addition to unblinded staff that are responsible for actions that the blinded evaluator cannot perform

Each site will designate a study team member to serve as the blinded evaluator, who will not know the group to which each subject is randomly assigned. [redacted] The subject and the blinded evaluator will

	be blinded to the study assignment. Each site will also designate study staff that will remain unblinded. The unblinded staff will be responsible for actions that the blinded evaluator cannot perform, [redacted]
Number of Sites	Up to 25 sites
Number of Subjects	[redacted] the trial will be planned with a maximum sample size of 126 subjects. [redacted]
Inclusion Criteria ***(assessed at Eligibility Visit 1)***	• At least 21 years old • Unilateral [redacted] lower extremity amputation • Healed amputation and healthy residual limb based upon the investigator's evaluation • Post-amputation pain score at baseline ≥ [redacted] on a scale of 0-10 (BPI-SF, question #5) in at least one region of post-amputation pain • Able to understand and willing to take part in study and comply with all study requirements
Additional Inclusion Criteria ***(assessed prior to the Testing Visit)***	• Average post-amputation pain intensity score of ≥[redacted] (determined by calculating the mean "average pain" collected in a 7-day diary, using Question #5 on the BPI-SF) in at least one region of pain
Exclusion Criteria	• Change of prescribed medications affecting pain within the past 4 weeks [redacted] • Beck Depression Inventory (BDI-II) score of > 20 • Body Mass Index (BMI) greater than 35 (height and weight obtained at Visit 1 without prosthesis) • Compromised immune system based on medical history [redacted] or other conditions that places the subject at increased risk in the opinion of the investigator • Uncontrolled Diabetes Mellitus Types I or II [redacted] • Implanted electrical stimulation device (e.g., spinal cord, DRG, nerve, or brain stimulator), or any active cardiac pacemaker/defibrillator • History of bleeding disorder (e.g., hemophilia) or subjects with active anticoagulation whose use or temporary modification for the lead placement procedure places the subject at increased risk in the opinion of the investigator. • History of valvular heart disease

	• Confounding conditions [redacted] • Central nervous system injuries and disorders [redacted] • Allergy to all local anesthetic agents [redacted] • Allergy to skin-contact materials [redacted] • History of recurrent skin infections • Botulinum toxin injection [redacted] in the affected limb • Steroid injection [redacted] in the affected limb • Subject has participated in any drug or device trial in the past 30 days • Subject has participated in previous [redacted] SPR Therapeutics-sponsored amputee pain feasibility trial or pilot study • Any other condition that may interfere with the ability to participate in a clinical trial [redacted] as determined by the Investigator • Prisoners
Additional Exclusion Criteria (verified after initial criteria verification)	• Pregnant (either urine dipstick or serum in females of reproductive potential)
Primary Safety Endpoint	• Study-related adverse device effect rates. Adverse device effects will be assessed at all visits.
Primary Clinical Endpoint	Pain Intensity: All amputees will record daily pain scores for RLP and PLP for the amputated limb in consecutive 7-day daily diaries using BPI-SF Question #5. [redacted] The percent change in RLP and PLP scores will be determined for each subject by taking the mean of the daily average pain intensity (BPI-SF Question #5) reported in the 7-day diary at baseline compared to the mean score for the same region(s) of pain reported over Weeks 5-8 of the therapy period (i.e. the average of all diary scores during this period). Data will be collected as described in the Schedule of Procedures (Appendix A). The primary endpoint compares the proportion of subjects in Group #1 relative to that in Group #2 that achieve ≥ 50% reduction in all areas of qualifying RLP and PLP from baseline to Weeks 5-8 of the therapy period, [redacted]
Secondary Endpoints	Several secondary endpoints will be collected to evaluate what effect, if any, the interventions have on each measure. The following secondary efficacy endpoints will be collected:

	• Individual components of the primary endpoint – proportion of success (≥ 50% reduction) for RLP and PLP evaluated separately for each region at 5-8 weeks after SOT. • Treatment effect for average pain intensity at 1-4 weeks after SOT, compared to the effect in weeks 1-4 for Group #2 • Durability of the treatment effect for average pain intensity at 3, 6, and 12 months after SOT, compared to the effect in Month 3 for Group #2. • Pain interference (BPI-SF Question #9) • Pain disability (Pain Disability Index) • Pain medication usage • Pain Catastrophizing Scale (PCS) • Global impression of change (Patient Global Impression of Change (PGIC))
[redacted]	[redacted]

2.0 General Information

Study Title The SNAP Trial: SPRINT® peripheral nerve stimulation for the treatment of Neuropathic post-Amputation Pain in a randomized, double-blinded, placebo-controlled, multicenter trial

2.1 Sponsor Name and Address

SPR Therapeutics
22901 Millcreek Boulevard, Suite [redacted]
Cleveland, OH 44122
Phone: 216-378-9108
Fax: 216-803-0777

2.2 Name of the Test Device

SPRINT® Peripheral Nerve Stimulation (PNS) System.

2.3 Cleared Indication for Use

The PNS System received 510(k) clearance with the following Indication for Use.

The SPRINT Peripheral Nerve Stimulation (PNS) System is indicated for up to 60 days in the back and/or extremities for:

- Symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain;
- Symptomatic relief of post-traumatic pain;
- Symptomatic relief of post-operative pain.

The SPRINT PNS System is not intended to treat pain in the craniofacial region.

2.4 Study Objective

The study objective is to gather post-market data regarding the safety and effectiveness of the PNS therapy compared to a placebo effect in the treatment of neuropathic pain following amputation.

2.5 Funding

The proposed study is funded by the sponsor and supported in part by the Department of Defense (DoD) U.S. Army Medical Research and Materiel Command, Congressionally Directed Medical Research Programs, Joint Warfighter Medical Research Program W81XWH-16-JWMRP. The contract number is W81XWH-17-C-0019.

3.0 Introduction and background

3.1 Introduction

Many amputees suffer from neuropathic pain and present treatment methods are often unsatisfactory

Amputation results in pain in almost all patients and up to 70%-80% of patients have significant chronic pain[1]. Many amputees experience neuropathic pain in their residual limb (also called stump pain) (68-76% of amputees) and many also report neuropathic pain in their phantom limb (72-85% of amputees) [1-4]. Moderate to severe pain in either (or both) location(s) can be extremely debilitating to amputees, significantly decrease their quality of life, increase their risk of depression, and negatively affect their inter-personal relationships and their ability to return to work[5-7]. Although residual limb pain (RLP) and phantom limb pain (PLP) have traditionally been viewed and treated clinically as distinct mechanisms, they can both be considered manifestations of neuropathic pain following a common nerve injury event. Supraspinal and spinal mechanisms are generally considered to have a larger contribution to PLP, while peripheral mechanisms play a larger role in RLP[8-12]. Conventional treatments are typically only effective for one type of pain while less successful or ineffective for the other[13-18]. For example, intravenous lidocaine, denervation using botulinum toxin A, and pulsed radiofrequency reduce RLP but are less effective for PLP[8]. Because both RLP and PLP contribute to the debilitating effects of post-amputation pain, treatments are needed that address both these components of neuropathic pain following amputation. Present methods of treatment, which are primarily medications, are often unsatisfactory in reducing post-amputation pain, have unwanted side effects, and can often lead to addiction. Furthermore, rising levels of opioid addiction emphasize the need for non-opioid pain therapies[19].

Electrical stimulation can treat neuropathic pain, but conventional methods are too cumbersome, complex, or invasive, which limits their use in clinical practice

Electrical stimulation can be an effective method for treating chronic neuropathic pain, but conventional methods of implementation have practical limitations that prevent widespread use. Transcutaneous electrical nerve stimulation (TENS) systems require daily placement of skin surface electrodes, and are generally considered to be too cumbersome and impractical for daily use, resulting in poor compliance with treatment. Implanted spinal cord stimulation (SCS) systems require invasive lead implantation in the spinal column. SCS systems often have problems with lead migration, resulting in either the need for frequent reprogramming or clinical failure.

Published studies indicate that peripheral nerve stimulation can be very effective in treating many types of neuropathic pain, including post-amputation pain[20-27]. In case studies, electrical stimulation of the brachial plexus (n = 2 patients), the sciatic nerve (n = 2 patients), and the femoral nerve (n = 1 patient) with cuff electrodes produced immediate and lasting relief of post-amputation pain in amputees[20, 23, 28]. In other case studies, peripheral nerve stimulation has a reported success rate of over 80% and can almost completely eliminate pain in a majority of patients, but the traditional method of surgically placing the lead is time consuming and complex, which greatly limits its use[20-22, 24, 25]. Thus, the major limitation of traditional methods of peripheral nerve stimulation (PNS) is the need for a simple method of placing electrode leads quickly and easily in proximity to the target nerves.

The present study will collect evidence to support the safety and effectiveness of stimulating the nerves innervating the area of pain to produce greater pain relief than the placebo effect

[redacted]

[redacted] The present study proposes to gather data on the safety and clinical effectiveness [redacted] to reduce neuropathic pain after amputation using a randomized, double-blinded, placebo-controlled, multicenter study of the SPRINT Peripheral Nerve Stimulation (PNS) System.

[redacted]

In all subjects, leads will be placed [redacted] Subjects will use the stimulation system for 8 weeks: in Group #1, the system will deliver electrical stimulation [redacted] while in Group #2 the system will deliver sham (placebo) stimulation. [redacted]

3.2 Background

Neuropathic pain after amputation is a significant problem that is not adequately addressed by conventional treatment options

Amputation results in chronic pain in up to 70%-80% of patients[1]. Neuropathic pain after amputation is multifaceted and can include residual limb pain (RLP) and phantom limb pain (PLP). RLP is sensed in the portion of the limb that remains after amputation, and PLP is perceived in the portion of the limb that has been removed. Approximately 72-85% of amputees have PLP and 68-76% of amputees have RLP[1-4]. Many amputees with severe residual limb pain also have severe phantom limb pain, and both RLP and PLP are believed to be of neuropathic origin, but historically they have been assessed and treated independently[29], often with limited long-term success. Consequently, chronic neuropathic pain can be severe and debilitating to a large proportion of persons with amputations, who will often progress through a battery of management techniques and procedures without finding relief from their pain[12, 30].

Neuropathic pain can lead to deteriorating quality of life, frustration, and depression

Approximately 1.7 million individuals in the United States are living with an amputation, and approximately 185,000 individuals undergo an amputation each year[1, 31]. The severity and high incidence of neuropathic pain after amputation makes it a significant medical problem[2, 3, 32]. The pain often leads to discouragement, anger, embitterment, and general suffering[12]. Neuropathic pain frequently causes further disability and greatly reduces the quality of life for amputees[12, 33]. Post-amputation pain is associated with depression and depressed mood, and the incidence of depression is 3-5 times greater in amputees than in the general population[1, 7]. In amputees with moderate to severe pain, it is frequently the pain following amputation rather than the loss of a limb that most impacts the activities of daily living, prevents completion of simple tasks, and correlates most negatively with return to employment[34-36].

Conventional methods of medication, injections, physical therapies, psychological strategies, and surgery are unsatisfactory in managing neuropathic pain following amputation

Historically, many techniques have been developed to treat post-amputation pain, but none of them were consistently successful and all of them were ultimately insufficient[2, 3, 32, 37, 38] (Table 1). Presently, patients may be managed with medications, but approximately a third of amputees still report severe residual and phantom limb pain, as indicated by an intensity of $\geq$7 on a scale of 0-10 where 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine".

Non-opioid analgesics, such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDS), have relatively minor side effects and are commonly used for several types of pain. However, they are not specific to pain following amputation and are rarely sufficient in managing moderate to severe chronic neuropathic pain [12, 32, 39].

The use of opioid analgesics showed limited success in a few trials, but the data are limited and few amputees achieved consistent long-term pain relief from opioids[12, 32, 40]. Opioids carry the risk of addiction and side effects, such as nausea, confusion, vomiting, hallucinations, drowsiness, dizziness, headache, agitation, and insomnia. Several trials of multiple opioids have failed to show statistically significant improvement in phantom pain[12, 32, 41]. Rising levels of opioid addiction and associated socioeconomic burdens have also prompted a reexamination of prescribing practices and highlight the need for non-opioid pain management options[19].

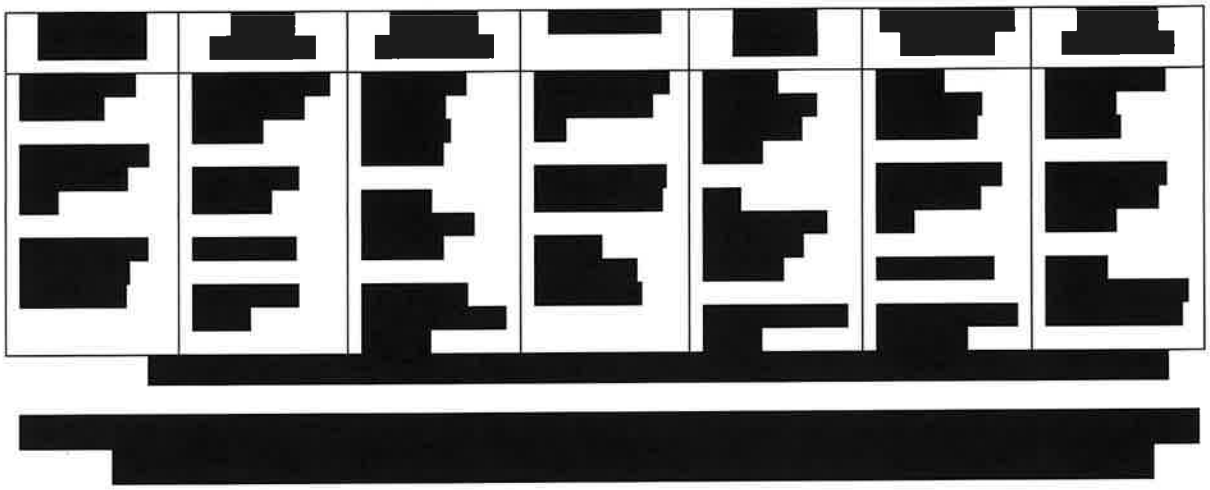
Adjuvant medications including antidepressant and antiepileptic medications are often used for neuropathic pain, but their use for chronic post-amputation pain is based primarily on anecdotal evidence and there are few controlled clinical trials to support their efficacy for residual limb pain and phantom limb pain[12, 42]. In small trials, some benefit has been seen with administering dextromethorphan or calcitonin[43, 44], but the correct dosage has not yet been determined and there have been few supporting trials to demonstrate efficacy with these medications[12, 32].

Anesthetics are useful in reducing the acute post-operative pain that immediately follows amputation, but they are rarely useful in providing lasting relief[32]. Delivering analgesia via a peripheral nerve catheter is safe but does not prevent neuropathic pain after amputation and is therefore typically limited to acute pain[12, 45, 46].

Physical methods such as adjusting the prosthesis may be helpful, but only if the pain is due to poor prosthetic fit. Other physical treatments, including acupuncture, massage, pulsed radiofrequency (local application of energy to temporarily block nerve conduction), and percussion or heating/cooling of the residual limb, have few complications but also have limited data to support their use and have not been well accepted clinically[12, 47-49].

Psychological strategies, such as biofeedback and psychotherapy, may be used as an adjunct to other therapies but are seldom sufficient, not specific to neuropathic pain after amputation, and there are few studies demonstrating their efficacy[39, 50]. Mirror-box therapy (use of a mirror image of the non-amputated limb to create an artificial visual image for the patient to perceive movement of the phantom limb) has demonstrated mixed results and is not widely used in clinical practice[51-53].

Many surgical procedures have been attempted, but few are successful and many are contraindicated for the majority of amputee patients[12]. Neuromas (a tangled mass of sensitive nerve endings) develop when a nerve is cut, and often form following amputation. Neuromas are implicated in neuropathic pain after ampuation, and there have been numerous attempts to remove them surgically, but generally the pain relief only lasts for the few weeks that it takes for a new neuroma to form[39, 54, 55]. Overall, any surgical procedure has a greater chance of long-term failure than success, and neuroablative procedures carry the additional risk of producing deafferentation pain[12, 32]. Thus, present medical treatments of neuropathic pain after ampuation are inadequate, and many sufferers resort to living with pain that is poorly controlled with medications.



TENS can be effective but has low long-term rates of success and compliance

Transcutaneous electrical nerve stimulation (TENS) is a commercially available treatment for pain and may be successful in reducing post-amputation pain. TENS systems are external neurostimulation devices that use electrodes placed on the skin surface to activate target nerves below the skin surface. When stimulation evokes paresthesias that cover the target area, it confirms that electrode placement and stimulus intensity should be sufficient to activate the target nerve and ultimately provide pain relief[20-22]. However, when larger stimulus intensities are used in an attempt to activate the deeper nerves, it becomes more likely that cutaneous nociceptive fibers will be activated, causing the patient to feel pain at the skin surface. TENS has a low rate of serious complications, but it also has a relatively low (< 25%) long-term rate of success, which is likely related more to a decrease in patient compliance over time rather than a physiological change in the mechanism of action[20, 39, 56]. Most patients ultimately decide to discontinue use of the system because of the pain at the skin surface, the need to correctly replace surface electrodes daily, the awkwardness of the external system and cables, and/or the interference of the external system with their daily activities[23, 39, 56, 57].

SCS is often successful initially but loses efficacy as the lead migrates away from its initial location

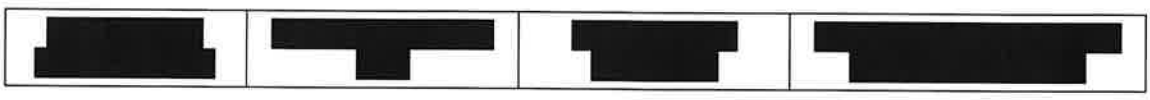
Spinal cord stimulation (SCS) systems are FDA-approved, commercially-available, implantable neurostimulation devices marketed in the United States that involve the placement of leads in the epidural space for the treatment of pain. Similar to TENS, when SCS evokes paresthesias that cover the target area, it confirms that the location of the electrode and the stimulus intensity should be sufficient to provide pain relief. Pain relief can be excellent initially, but maintaining long-term sufficient paresthesia coverage is often a problem as the lead migrates within the epidural space[58-60].

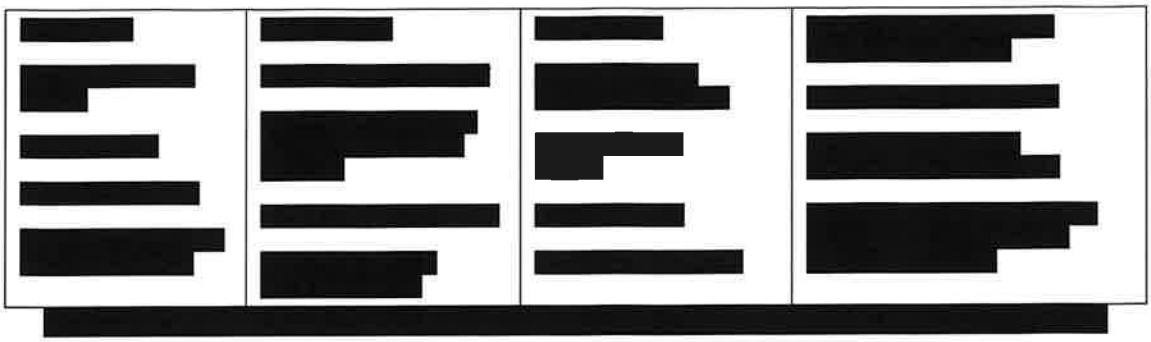
Lead migration is a common complication for spinal cord stimulators occurring in up to 10-35% of the cases[26, 59, 61-64]. When the lead migrates, the active contact moves farther from the target fibers and loses the ability to generate paresthesias in the target area. SCS systems attempt to address this problem by using leads with multiple contacts so that as the lead moves, the next contact in line can be selected to become the active contact. It is common for patients to return for reprogramming as the lead migrates[26], and up to 88% of patients may require one or more reprogramming visits after initial implantation[59]. Of patients with adequate paresthesia coverage, up to 83% report successful pain relief at 6 months, but pain relief is often lost over time as paresthesia coverage changes[59]. The option of reprogramming the contacts has improved the chances of regaining some pain relief, but it is often difficult to regain the same paresthesia coverage and pain relief obtained during the initial lead placement, frequent reprogramming is required, and revision surgery may still be required in 11-46% of the cases[59-62, 64, 65]. A review of 289 patients receiving SCS systems indicated 46% of the patients required hardware revision and 23% of patients required multiple revisions with poor pain relief and migration noted as the most common reasons for revision[64]. Lead migration often corresponds with the loss of paresthesia coverage and loss of pain relief with SCS, suggesting that if a lead can be placed in an alternate peripheral location where it is less likely to migrate and where stimulation is applied more directly to the target pain location, then stimulation can maintain paresthesia coverage and achieve sustained pain relief.

Though SCS has been used for decades, many physiatrists who treat amputees with chronic pain still consider SCS to be an invasive procedure for which the low (23-32%) long-term success rate does not justify the risks and potential complications. As a result, amputees are often not referred to specialists to receive SCS systems[32, 57, 66, 67].

Electrical stimulation of the brain is seldom used to treat post-amputation pain

In some cases, motor cortex stimulation (MCS) and deep brain stimulation (DBS) have reduced post-amputation pain by at least 50%, but the data is limited to small numbers of patients[68-70]. Despite the promising preliminary results, the authors and proponents of these studies caution that it is very difficult to predict which patients will benefit from treatment and that further study is still needed to test the effectiveness under double-blind conditions[68, 69]. Due to cost and invasiveness, it is unlikely that either MCS or DBS will be recommended for neuropathic pain following amputation until additional clinical trials are performed to refine the patient selection criteria and confirm the long term effectiveness[12, 32, 68, 69].





Electroconvulsive therapy is rarely used to treat residual limb pain and phantom limb pain

There have been very limited reports on the use of electroconvulsive therapy (ECT) in the treatment of neuropathic pain after amputation. Small studies have described some benefit in amputee patients after all other options have been exhausted, but ECT is typically not recommended for amputee patients[32, 71].

High (> 1 kHz) frequency stimulation of peripheral nerves through a nerve cuff is not FDA-approved for pain relief in amputees and it is difficult to implement and maintain clinically

Under controlled (laboratory) conditions, high frequency (e.g. > 1kHz) stimulation has been shown to decrease transmission of peripheral nerve signals[72, 73]. Early studies suggested high frequency stimulation of peripheral nerves reduced neuropathic pain, including residual and phantom limb pain[74, 75]. Temporarily decreasing afferent signals from the peripheral source (e.g. neuroma) may decrease pain but does not mediate the central mechanisms that develop during central sensitization in the chronic state. Thus, short-term high-frequency nerve stimulation is unlikely to be more effective in relieving neuropathic pain long-term than direct application of anesthetic to the peripheral nerve, which has been shown to be ineffective and is seldom used in relieving persistent pain following amputation[12, 45, 46]. Additionally, long-term high-frequency stimulation of peripheral nerves through a nerve cuff requires invasive surgery to implant a pulse generator and place electrodes around the nerve[74], and it may be difficult to maintain sufficient pain relief in practice in ambulatory patients in their home environment.

3.2.2 Neuropathic pain following amputation may be reduced with peripheral nerve stimulation (PNS)

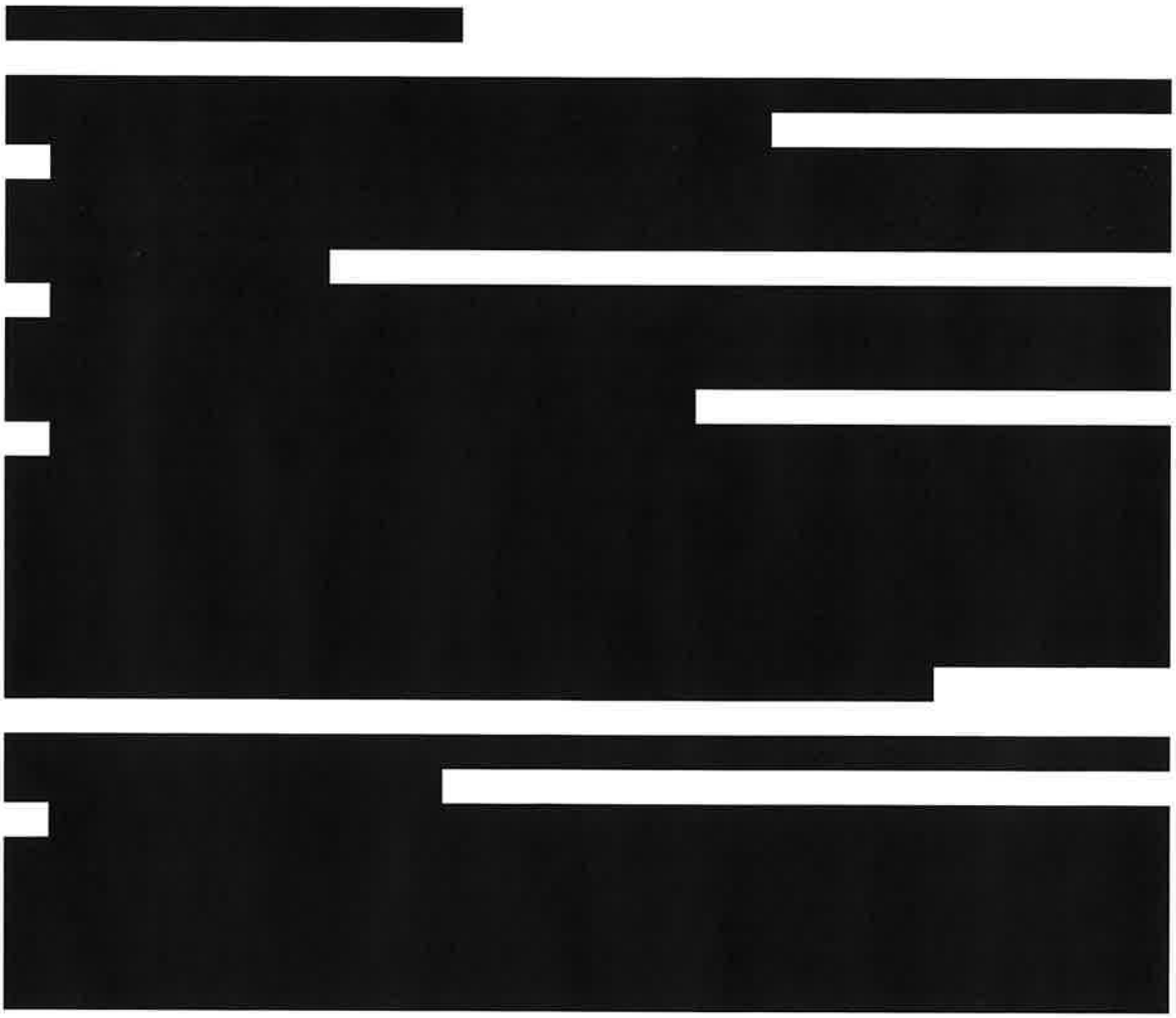
Peripheral nerve stimulation (PNS) can provide dramatic pain relief but the existing methods of implanting the lead are time consuming and complex, limiting widespread use

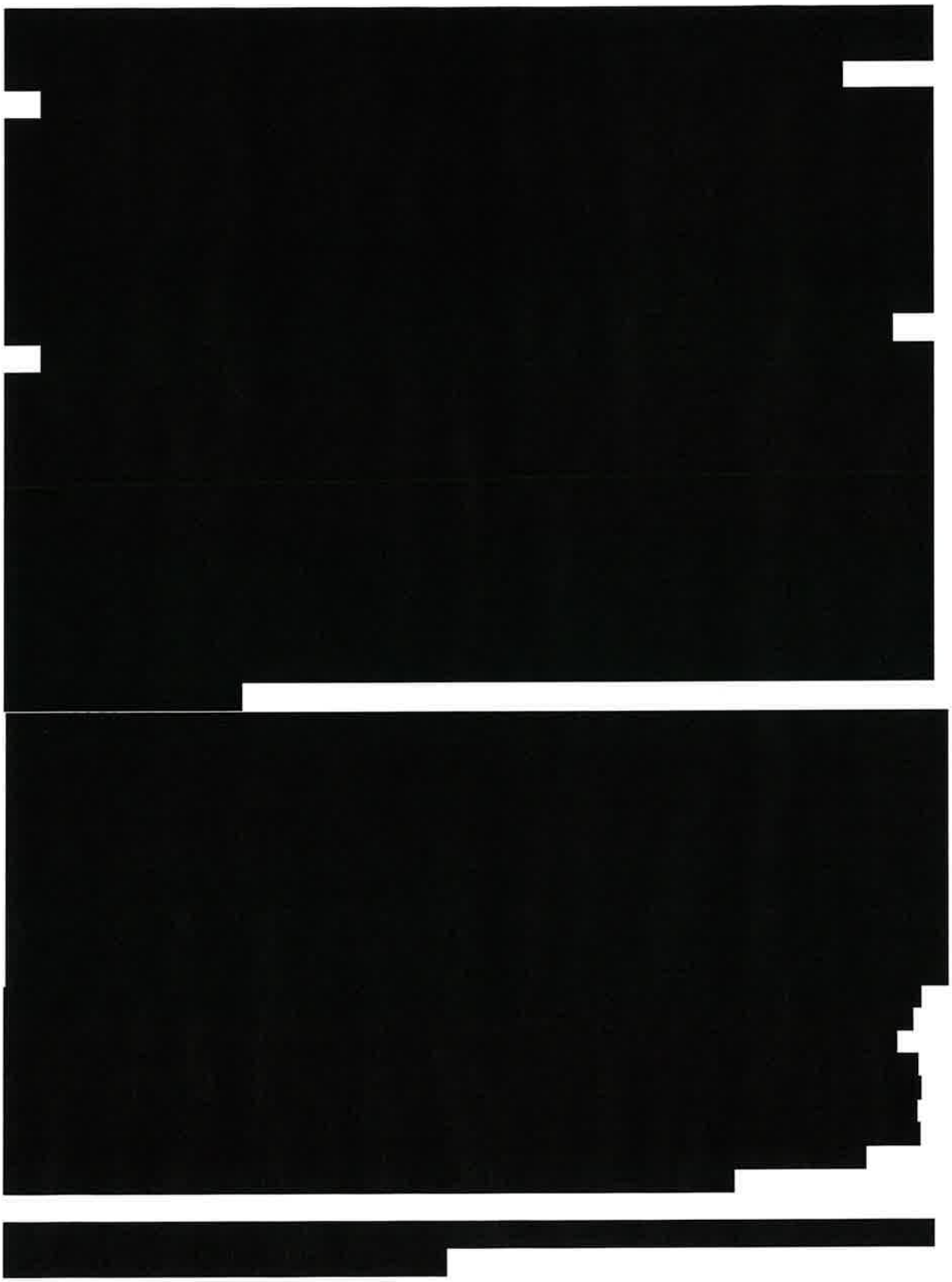
Direct stimulation of peripheral nerves with an implanted lead connected to an implantable pulse generator (IPG) is a viable long-term solution and has been effective in reducing pain with high (up to 80%) success rates[76, 77]. Peripheral nerve stimulation (PNS) has been shown to provide dramatic pain relief, improve sleep, increase quality of life, allow a significant percentage (20-50%) of patients to return to work, and reduce or eliminate dependence on opioid analgesia[78, 79]. Of the 80% of patients who receive benefit, approximately 75% of them report almost complete pain relief, and the remaining 25% report significant pain relief[76, 77]. Of 117 patients receiving PNS who were followed up to 53 months, over 65% of them reported an increase in their activities of daily living and more than 75% were satisfied with therapy[80]. When followed long term, over 70% of patients maintained pain relief up to 4 years, and over 60% of patients followed up to 9 years reported long-term pain relief[78, 80].

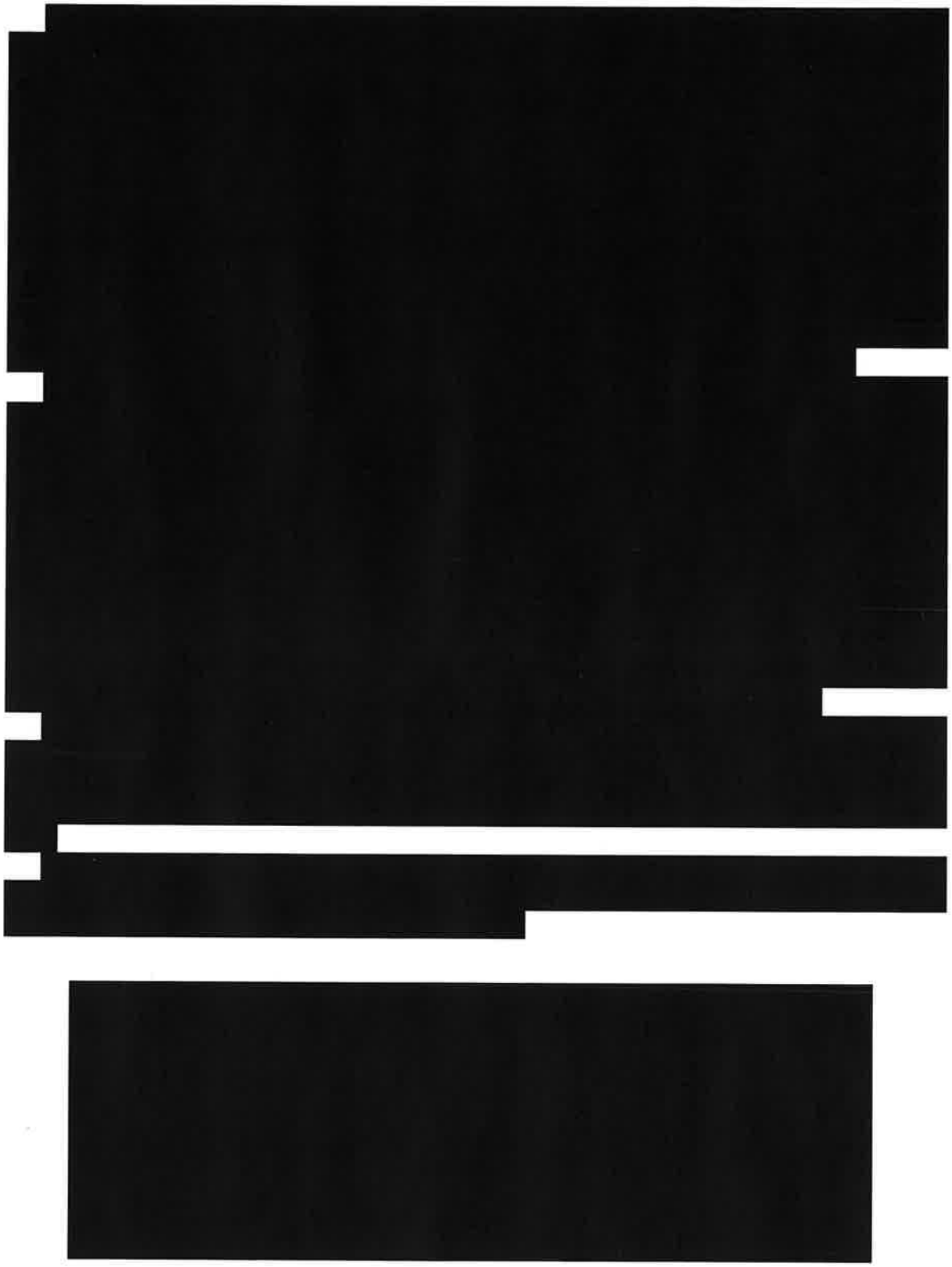
PNS is regarded as very effective in treating many types of neuropathic pain, including residual and phantom limb pain[20-26]. In case studies, electrical stimulation of the brachial plexus (n = 2 upper extremity amputee patients), the sciatic nerve (n = 2 lower extremity amputee patients), and the femoral nerve (n = 1 lower extremity amputee patient) with cuff electrodes has produced immediate and lasting relief of residual and phantom limb pain in amputees[20, 23, 28].

Though PNS has a high success rate (up to 80%), the traditional method of surgically placing the lead is time consuming and complex because it requires careful open dissection of surrounding tissue to identify and prepare the target nerve for implantation of the electrode. At present, the extended time and complexity of the existing methods of surgical placement of the lead greatly limits the use of PNS outside of academic institutions[20-22, 24, 25].

The previous feasibility and pilot studies demonstrated that the proposed method of percutaneous PNS provides substantial pain relief, it could be performed quickly and without surgery[27], and it provides pain relief that is greater than the placebo effect (Section 3.2.3 Summary of feasibility study and Section 3.2.4 Summary of pilot study). The present randomized placebo-controlled trial will gather additional information on the safety and effectiveness of the proposed method of PNS to provide relief of neuropathic pain after amputation.







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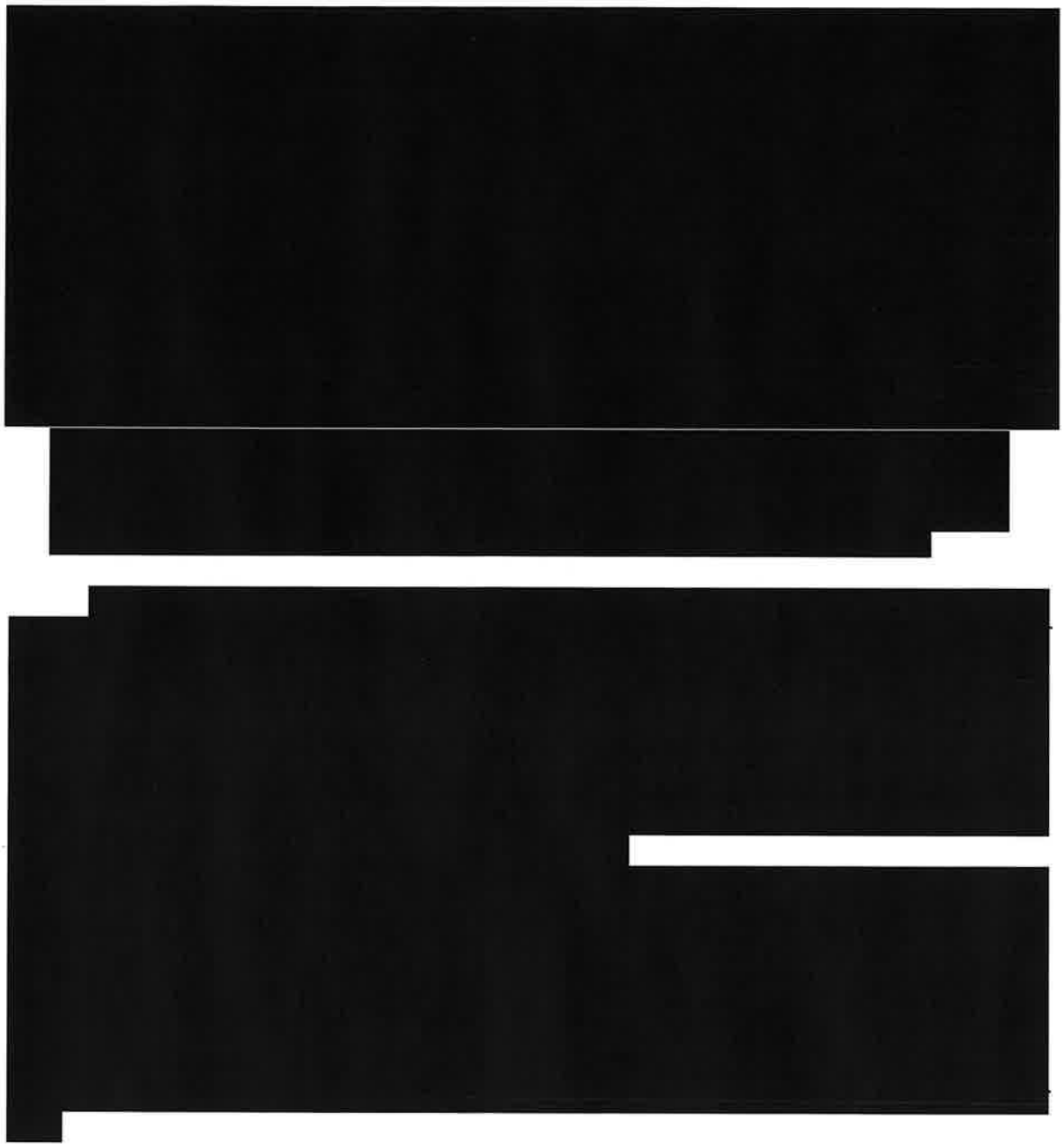
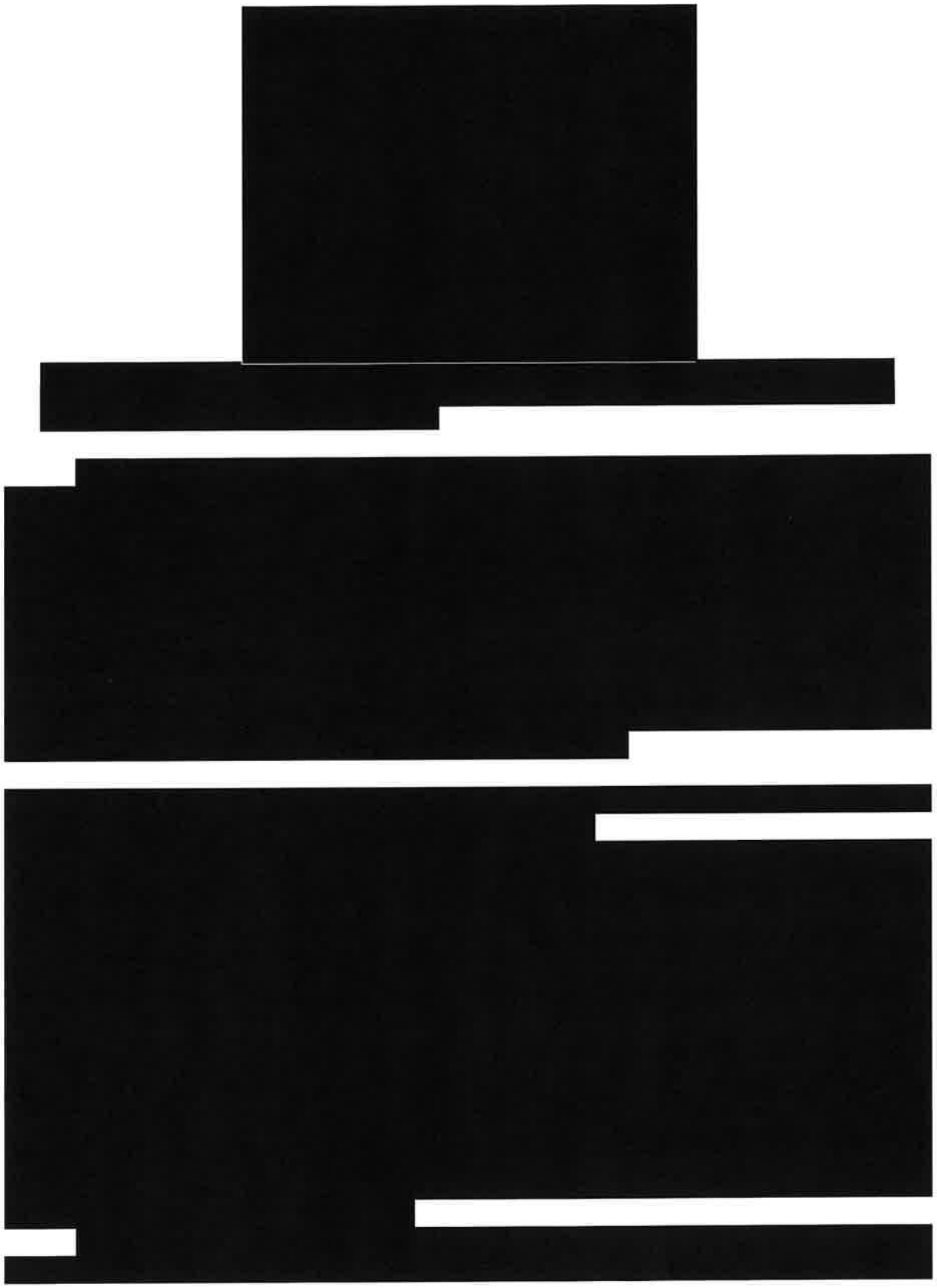




[redacted]

3.2.5 The conditions required to provide pain relief with PNS are well understood

PNS is believed to reduce neuropathic pain by decreasing transmission of pain signals in the central nervous system[88, 89]. The conditions and stimulus parameters needed to reduce neuropathic pain via PNS, residual and phantom limb pain in particular, are well known and include comfortable sensations (paresthesia) evoked by stimulation. [redacted]

Gate-control theory was proposed by Melzack and Wall[89, 90] to explain how activation of large myelinated fibers can inhibit the transmission of pain signals (and 'close the gate') from the spinal cord to higher centers in the central nervous system, which results in a decrease in the perception

of pain. This theory is still widely accepted today and is used to explain the mechanism through which spinal cord stimulation achieves pain relief by activating the same myelinated sensory fibers as PNS (albeit from a different anatomical location)[91].

[redacted]

When sensations are evoked in the areas of greatest pain, it suggests that the neuroma contributing to the pain may also be receiving electrical stimulation, which can reduce the ongoing neural activity originating from the neuroma[94, 97].

Neuromas develop when a peripheral nerve is cut and the proximal portion produces new axon growth that forms a tangled mass as it fails to connect with the missing distal portion of the nerve. All amputations produce neuromas and not all neuromas are painful, but neuromas are thought to be a substantial source of pain after amputation[12, 32, 98]. Neuromas may generate ongoing spontaneous activity[94], and the level of activity in afferent fibers innervating the region of pain has been linked to the level of pain[99]. In rats and rabbits, spontaneous and evoked activity has been recorded from neuromas, and the rate of activity increases when pressure is applied to the neuroma[94, 100]. Injection of gallamine, which increases neuroma activity, increases pain, and injection of lidocaine, which decreases neuroma activity, decreases pain in amputees[98, 101, 102]. Spontaneous activity has been recorded via intraneural microelectrodes in the nerves innervating the regions of phantom pain in amputee patients, and mechanically tapping the neuroma increased both the pain and the afferent activity[99].

[redacted]

[redacted]

4.0 Study Endpoints

4.1 Overview

Outcome measures will be administered to each subject in Group #1 (8 weeks of active stimulation) and Group #2 (8 weeks of sham stimulation) at Baseline and at specified follow-up visits as described in Appendix A. To support the study endpoints, the following outcome measures will be used:

1. Diary
   - Average RLP
   - Average PLP
   - Medication affecting pain, including reason for use
2. Brief Pain Inventory, Short Form (BPI-SF)
3. Pain Disability Index (PDI)
[redacted]
5. Patient Global Impression of Change (PGIC)
6. Pain Catastrophizing Scale (PCS)
[redacted]

4.2 The primary efficacy endpoint will be average neuropathic pain

Amputation results in chronic post-amputation pain in up to 70%-80% of patients[1]. Neuropathic pain is particularly prevalent after amputation, and can include pain both in the residual limb (68-76% of amputees) and phantom limb (72-85% of amputees)[1-4]. The presence of RLP is highly correlated with reports of phantom pain[2]; amputees are significantly more likely to experience RLP if they also experience PLP, and 66-70% of amputees report pain in more than one region[2-4]. Therefore, treatment that effectively reduces both RLP and PLP is of considerable importance because of the disability and reduced quality of life caused by neuropathic pain after amputation. Based on published and draft FDA Guidance pertaining to multiple endpoint analysis and patient-reported outcomes in pain studies, RLP and PLP are suitable to be considered as separate components in a single primary efficacy endpoint[103, 104], because reductions in RLP and PLP are of similar importance to patients, are likely to occur with similar frequency, and are likely to have roughly similar treatment effects (see Sections 3.2.3 and 3.2.4). [redacted]

- average neuropathic pain in the residual limb (i.e., residual limb pain (RLP)) from weeks 5-8 of the therapy period (in both Treatment and Control groups) compared to baseline in all qualifying regions of RLP
- average neuropathic pain in the phantom limb (i.e., phantom limb pain (PLP)) from weeks 5-8 of the therapy period (in both Treatment and Control groups) compared to baseline in all qualifying regions of PLP

All amputees will record RLP and PLP average pain scores (BPI-SF Question #5) for the amputated limb daily in the 7-day diaries. [redacted] Each pain region with a calculated mean of the "average pain" ≥ [redacted] in a limb that receives device(s) will qualify to be used in the primary outcome analysis for that subject. Each randomized subject must obtain ≥ 50% reduction in the qualifying regions of RLP during weeks 5-8 of the therapy period relative to the baseline scores to be considered a success in the RLP component of the primary endpoint. Similarly, each randomized subject must obtain ≥ 50% reduction in all qualifying regions of PLP during weeks 5-8 of the therapy period relative to the baseline scores to be considered a success in the PLP component of the primary endpoint. [redacted]

[redacted] subjects must be considered a success in both components to be considered a success overall in the primary endpoint analysis.

The primary endpoint of the study compares the proportion of successes of Group #1 (Treatment) relative to that of Group #2 (Control), [redacted]

4.3 Safety Endpoint

The primary safety endpoint is the occurrence and type of study-related adverse events, also known as adverse device effects (ADEs). All ADEs that occur during the study will be documented and analyzed. [redacted]

4.4 Secondary Efficacy Endpoints

Several secondary endpoints will be collected to evaluate what effect, if any, the interventions have on each measure:

- Analyses of the proportion of successes in Group #1 compared to Group #2 in the individual components of the Primary Endpoint (RLP and PLP analyzed independently) during Weeks 5-8 after the start of therapy (SOT)
- Durability of the treatment effect on average pain intensity (Primary Endpoint) at 3, 6 and 12 months after SOT
- Analysis of the proportion of successes in Group #1 compared to Group #2 during Weeks 1-4 after the start of therapy (Success overall, similar to the primary endpoint)
- Pain interference (BPI-SF Question #9) at 4 weeks, 8 weeks, and 3, 6, and 12 months after SOT
- Pain disability (Pain Disability Index (PDI)) at 4 weeks, 8 weeks, and 3, 6, and 12 months after SOT
- Global impression of change (Patient Global Impression of Change (PGIC) at 4 weeks, 8 weeks, and 3, 6, and 12 months after SOT
- Pain Catastrophizing Scale (PCS) at 4 weeks and 8 weeks after SOT
- Pain medication usage during Weeks 1-4 after the start of therapy, during Weeks 5-8 after SOT, and at 3, 6, and 12 months after SOT

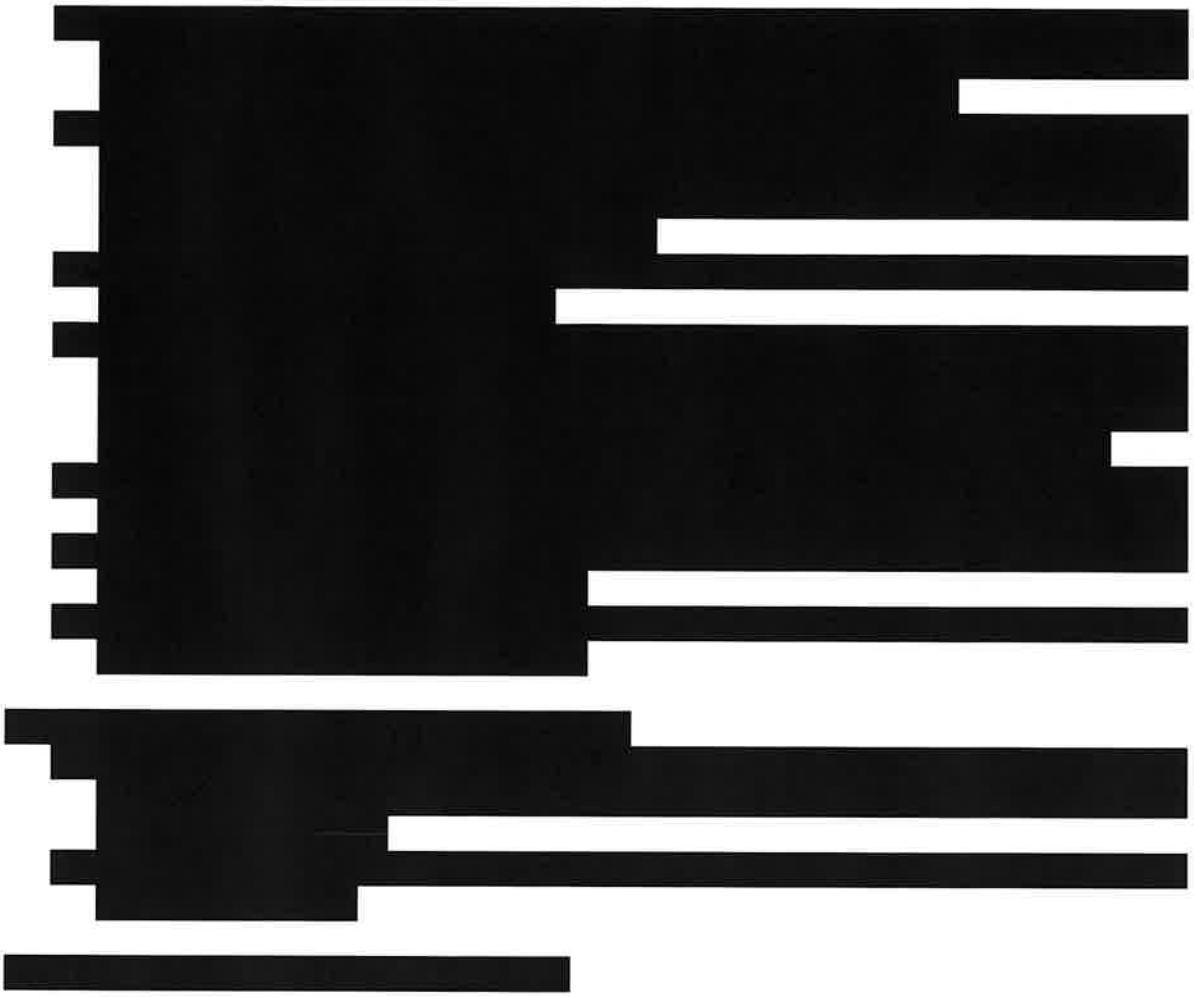
[redacted]

[redacted]

5.0 Device Description

5.1 Overview

This study utilizes two commercially available SPRINT® PNS Systems that will be referred to or labeled interchangeably; therefore, the study documents will reference the generic name of PNS System. [redacted]



[redacted]

6.0 Scope

6.1 Number of sites

Multi-center Study (up to 25 sites)

6.2 Number of subjects

The study will be planned with a maximum sample size of 126 subjects [redacted] Subjects will be randomized to either Group #1 or Group #2 [redacted] Subjects who sign an informed consent form and do not meet all study eligibility criteria, or that are not randomized, will be considered screen failures and not count against the number of enrolled subjects.

[redacted]

[redacted]

6.3 Study duration

[redacted]

7.0 Study protocol

7.1 Overview

This post-market study is a randomized, double-blinded, placebo-controlled, multi-center study to gather post-market data on the safety and effectiveness of peripheral nerve stimulation (PNS) therapy for the treatment of neuropathic pain following amputation.

7.2 Study population

Prospective subjects with neuropathic pain following amputation, including residual limb pain and/or phantom limb pain, will be screened for eligibility into the study using the Eligibility criteria listed in Section 7.4. [redacted]

7.3 Subject recruitment

Subjects with neuropathic pain following amputation will be recruited by the investigators, following all HIPAA guidelines, to ascertain their level of interest and willingness to take part in this project. [redacted]

7.4 Eligibility

Amputees who meet all of the inclusion and none of the exclusion criteria will be eligible to enroll in the study as subjects.

7.4.1 Inclusion criteria

- At least 21 years old
- Unilateral [redacted] lower extremity amputation
- Healed amputation and healthy residual limb based upon the investigator's evaluation
- Post-amputation pain score at baseline ≥ [redacted] on a scale of 0-10 (BPI-SF, question #5) in at least one region of post-amputation pain
- Able to understand and willing to take part in study and comply with all study requirements

7.4.2 Additional inclusion criteria (assessed prior to the testing visit)

- Average post-amputation pain intensity score of ≥ [redacted] in at least one region of pain

7.4.3 Exclusion criteria

- Change of prescribed medications affecting pain within the past 4 weeks [redacted]
- Beck Depression Inventory (BDI-II) score of > 20
- Body Mass Index (BMI) >35 (height and weight obtained at Visit 1 without prosthesis)
- Compromised immune system based on medical history [redacted] or other conditions that places the subject at increased risk in the opinion of the investigator
- Uncontrolled Diabetes Mellitus Types I or II, [redacted]
- Implanted electrical stimulation device (e.g., spinal cord, DRG, nerve, or brain stimulator), or any active cardiac pacemaker/defibrillator
- History of bleeding disorder (e.g., hemophilia) or subjects with active anticoagulation whose use or temporary modification for the lead placement procedure places the subject at increased risk in the opinion of the investigator.
- History of valvular heart disease
- Confounding conditions [redacted]
- Central nervous system injuries and disorders [redacted]
- Allergy to all local anesthetic agents such as lidocaine or previous reaction to anesthesia
- Allergy to skin-contact materials (stickers, bandages, tape etc.)
- History of recurrent skin infections
- Botulinum toxin injection [redacted] in the affected limb
- Steroid injection [redacted] in the affected limb
- Subject has participated in any drug or device trial in the past 30 days
- Subject has participated in previous [redacted] SPR Therapeutics sponsored Amputee Pain feasibility trial or pilot study
- Any other condition that may interfere with ability to participate in a clinical trial [redacted]
- Prisoners

7.4.4 Additional exclusion criteria (verified after initial criteria verification)

- Pregnant (either urine dipstick or serum in females of reproductive potential)

7.5 Concurrent medications and non-drug therapies

All interventions targeting pain control will be recorded in the Case Report Forms (CRF) and patient diaries.

Daily medications affecting pain will be permitted at levels established during baseline

All subjects will be permitted to continue use of all medications affecting pain throughout the study; however, dosages of these medications will be controlled and recorded during the study, as well as the reason for the medication usage. To be eligible for participation in the study, individuals will be required to have a stable medication history (i.e., not have added new medications or

changed the dose of medications affecting pain within the past 4 weeks) [redacted]

Supplemental OTC medications for unresolved neuropathic pain, and other pain

Subjects experiencing neuropathic pain (i.e., RLP or PLP) during the study that is not resolved by the therapy or baseline medications will be permitted to use one of the approved supplemental over-the-counter (OTC) medications per day. These supplemental OTC medications will also be permitted for subject use for other types of pain that may occur over the length of the study (i.e., headache, backache, toothache). [redacted] All medication use, including the reason why the medication was taken, will be documented [redacted]

Non-pharmacologic therapies in use during baseline will be permitted if they do not increase risk to the subject

Non-pharmacologic therapies, such as physical therapy or other rehabilitative services, that do not interfere with treatment or increase risk to the subject at the opinion of the investigator, are permitted if they are in use during baseline. [redacted]

[redacted]

7.6 Treatment plan

The study procedures for this protocol are classified according to the following time periods: Baseline, Screening and Lead Placement, Treatment, and Follow-up. During the 8-week therapy period, Group #1 will receive active stimulation while Group #2 will receive sham stimulation. Following the [redacted] follow up visit (Visit 13), Group #2 will [redacted] choose to participate in an optional cross over and receive active stimulation, or be discharged from the study. [redacted]

7.6.1 Visit 1 - Baseline

Individuals will receive a detailed explanation of study-specific procedures as well as the risks and benefits of participating in the study. The individual will be asked to sign the approved study consent during this visit. If the individual agrees to participate by signing the consent form, general inclusion/exclusion criteria will be verified and baseline information will be collected and recorded in the case report forms (CRF). Subject ID will be assigned.

[redacted]

The individuals who satisfy the preliminary criteria will be asked to complete a 7-consecutive-day baseline diary [redacted]

[redacted]

7.6.2 Visit 2 - Lead Placement and Testing

Following the baseline visit, individuals who qualify for lead placement (*i.e.,* meet the additional inclusion and exclusion criteria) will return to the clinic for placement of the percutaneous leads.

[redacted]

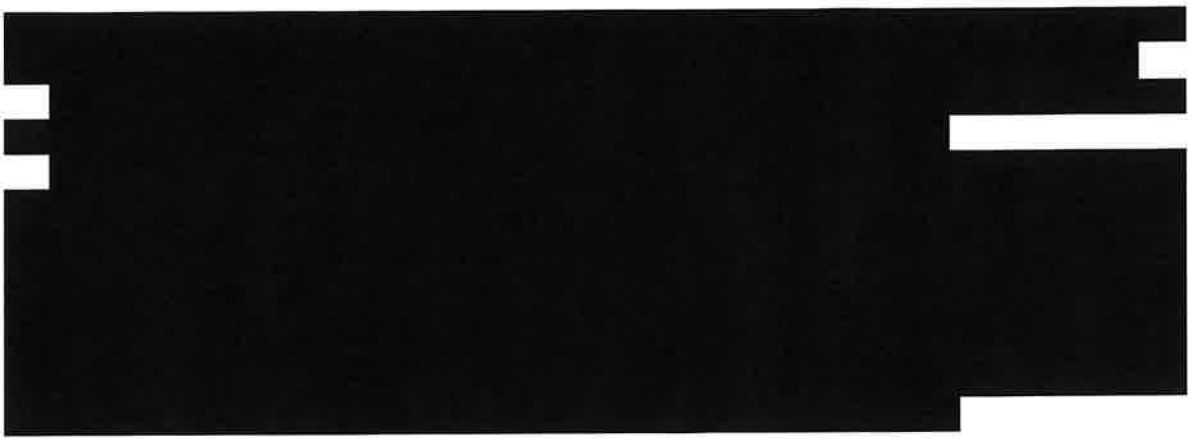
7.6.2.1 Randomization

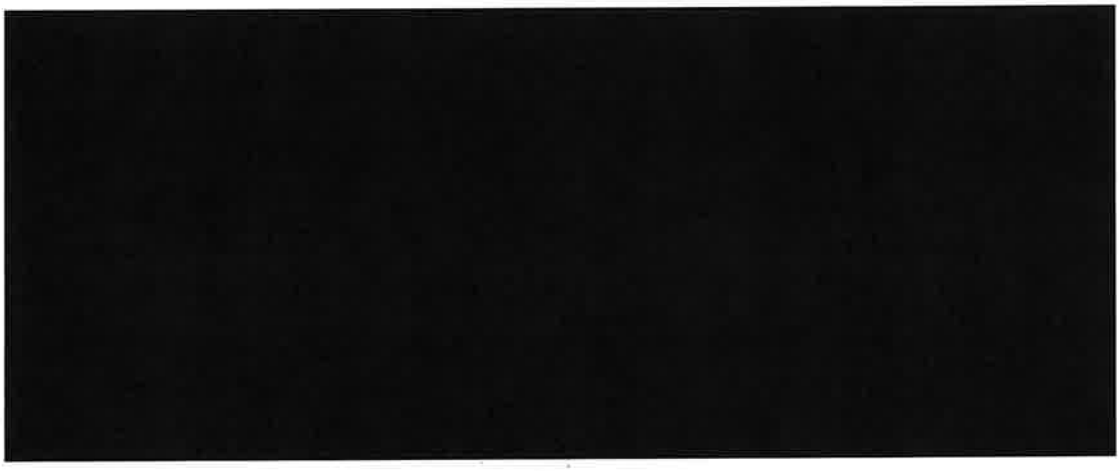
Qualifying individuals will be randomized to either Group #1 (Treatment) or Group #2 (Control) [redacted] Individuals will be blinded to their randomization assignment. [redacted]

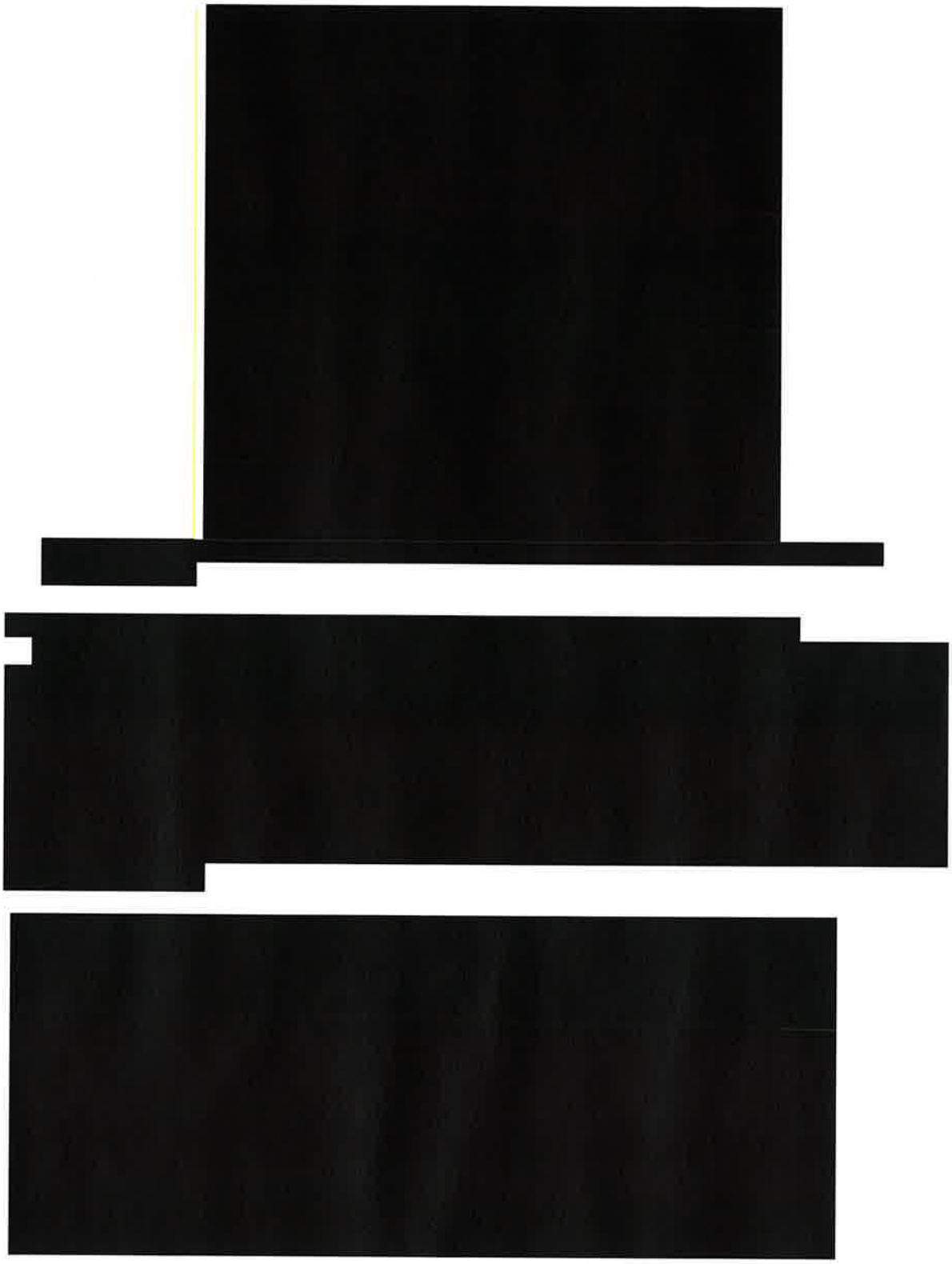
The group to which each subject is randomly assigned will remain concealed from the subject and the blinded evaluator until after Visit 13, but the randomization assignment will be made known to the unblinded study staff.

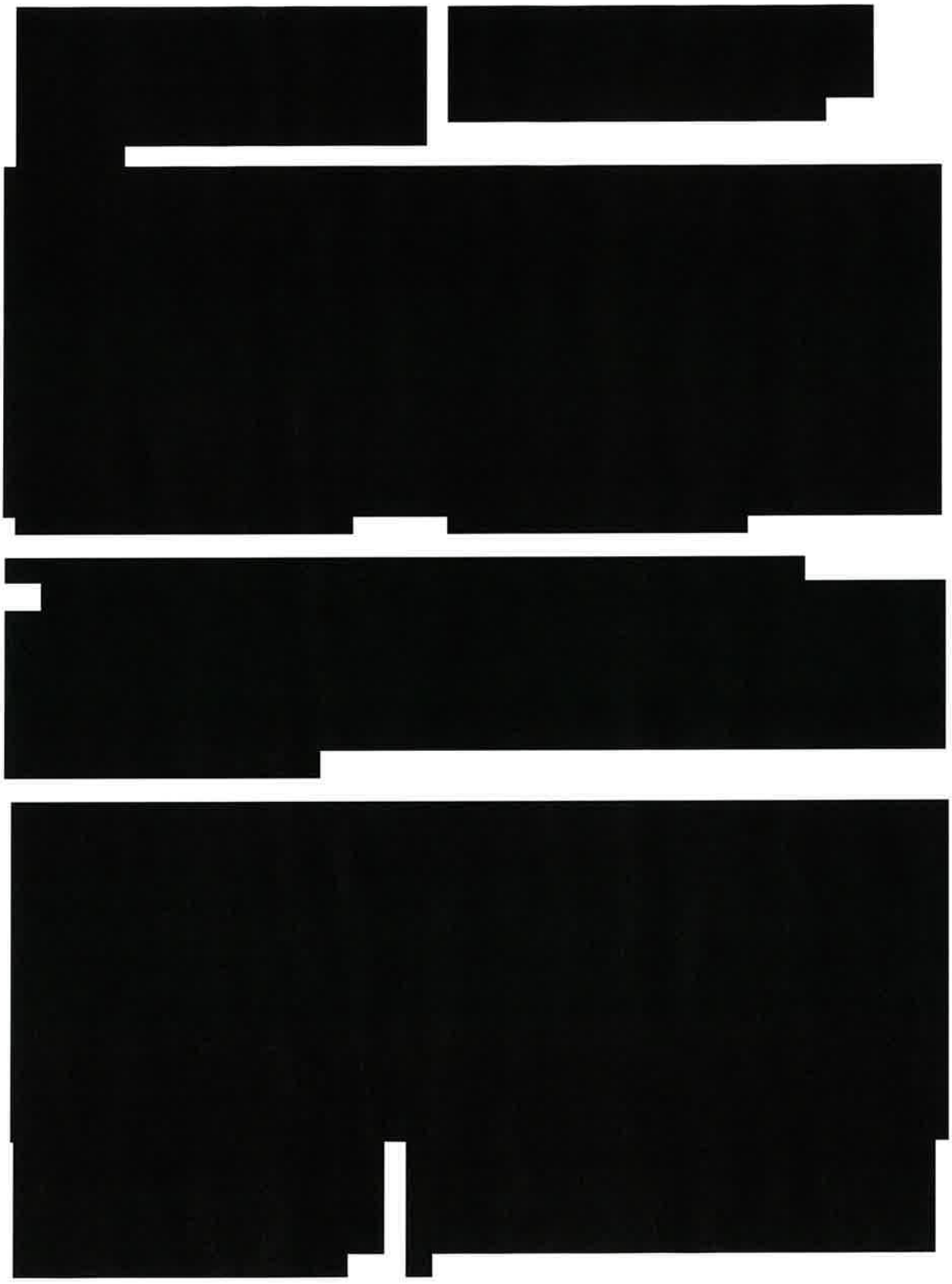
7.6.2.2 Leads will be placed [redacted]

After randomization assignment, subjects will be prepared for the lead placement procedure, [redacted]









[redacted]

7.6.2.5 Group #1:
Stimulus parameters will be programmed [redacted]

Group #2:

The procedure will be identical to Group #1 except that no active stimulation will be delivered. However, the study team and device will indicate that test stimulation is being delivered. [redacted]

7.6.2.6 Subject Disposition

At the end of Visit 2, there are three options:

1. Proceed to therapy period:

   If all leads were placed, the subject will be prepared to proceed to the therapy period. [redacted]

[redacted]

2. Return for another Visit 2:
   If there is not sufficient time [redacted] the investigator may present the subject with the option to return for a repeat lead placement visit.

3. Discharge from the study:
   If no leads are placed during Visit 2, and the subject does not wish to return for another lead placement procedure, the subject may be terminated from the study.

[redacted]

*7.6.2.8 **Therapy period***
At the end of Visit 2, subjects will be prepared to proceed to the therapy period
Subjects will be prepared to proceed to the therapy period.

[redacted]

[redacted]

7.6.3 Visit 3 - Telephone Follow-up

All subjects will receive a Telephone Follow-up 24 - 48 hours after each Visit 2 (Lead Placement) to query for any adverse device effects (ADE). All ADEs will be followed until resolution. [redacted]

7.6.4 Visit 4 – 1 Week Post Lead Placement

Subjects will return approximately 1 week after the final Visit 2.

[redacted]

7.6.5 Visit 5 – 2 Weeks Post Lead Placement

The subject will return approximately 2 weeks after the initial lead placement. [redacted]

7.6.6 Visit 6 – 3 Weeks Post Lead Placement

The subject will receive a Telephone Follow Up approximately 3 weeks after the initial lead placement [redacted]

7.6.7 Visit 7 – 4 Weeks Post Lead Placement

The subject will return approximately 4 weeks after the initial lead placement. [redacted]

7.6.8 Visit 8 – 5 Weeks Post Lead Placement

The subject will receive a Telephone Follow Up approximately 5 weeks after the initial lead placement [redacted]

7.6.9 Visit 9 – 6 Weeks Post Lead Placement

The subject will return approximately 6 weeks after the initial lead placement. [redacted]

7.6.10 Visit 10 – 7 Weeks Post Lead Placement

The subject will receive a Telephone Follow Up approximately 7 weeks after the initial lead placement [redacted]

7.6.11 Visit 11 – 8 Weeks Post Lead Placement: lead removal and end of treatment (EOT)

The subject will return approximately 8 weeks after the initial lead placement. [redacted] the leads will be removed for both groups, marking the end of treatment (EOT). [redacted]

[redacted]

7.6.12 Visit 12 – conducted 1 week after lead removal as a follow-up visit

Subjects will receive a Telephone Follow Up one week after the removal of percutaneous leads at the end of treatment. [redacted]

7.6.13 Visit 13 – Follow-up visit 3 months after start of treatment (SOT)

[redacted]

Following the completion of all outcome measures at Visit 13, subjects will be informed of their group assignment. Group #1 subjects will continue with follow-up Visits 14-16. Group #2 subjects will be given the option to discharge from the study, or crossover to receive active stimulation for an 8-week therapy period. [redacted] Group #2 subjects that choose to cross over to receive stimulation will continue with Visits C1-C4, then follow-up Visits C5-C8.

7.6.14 Visit C1: Crossover Lead Placement, Group #2

Visit C1 is similar to the lead placement at Visit 2. [redacted]

Leads will be placed [redacted]

The stimulation parameters will be set [redacted]

For Group #2 subjects who received replacement leads at this visit, there are three options:

1. Proceed to therapy period:

   [redacted] the subject will be prepared to proceed to the therapy period. [redacted]

[redacted]

2. Return for another Visit C1:
   If there is not sufficient time [redacted], the investigator may present the subject with the option to return for a repeat lead placement visit.

3. Discharge from the study:
   If no leads are placed during Visit C1, and the subject does not wish to return for another lead placement procedure, the subject may be terminated from the study.

7.6.15 Visit C2 – 2 Weeks Post Lead Placement, Group #2

Subjects will return approximately 2 weeks after the final Visit C1 Lead Placement. [redacted]

7.6.16 Visit C3 – 4 Weeks Post Lead Placement, Group #2

The subject will return approximately 4 weeks after the crossover lead placement. [redacted]

7.6.17 Visit C4 – 8 Weeks Post Lead Placement, Group #2

The subject will return approximately 8 weeks after the crossover lead placement. [redacted]

7.6.18 Follow-up visits for Group #1: Visit 14 (6-mo after SOT), Visit 15 (9-mo after SOT), Visit 16 (12-mo after SOT)

For Group #1 subjects, Visits 14-16 will occur approximately 6 months, 9 months, and 12 months after the start of treatment. [redacted]

7.6.19 Follow-up visits for Group #2: Visit C5 (3 months after start of crossover treatment (SOCT)), Visit C6 (6 months after SOCT), Visit C7 (9 months after SOCT), Visit C8 (12 months after SOCT)

Group #2 subjects that crossed over and completed stimulation therapy (Visits C1-C4) subject will receive a Telephone Follow Up approximately 3, 6, 9, and 12 months after the crossover lead placement [redacted]

[redacted]

7.6.21 Study Visit Windows

The acceptable windows for each visit are listed in Table 5. The study visit windows in Table 5 are guidelines, but every effort should be made to collect all study data, even if out of window.

[redacted]

Table 5 Study Visit Windows

Visit Number	Visit Name	Window
n/a	Consent	[redacted]
1	Baseline	
2	Lead Placement (SOT)	
3	Telephone Follow-up	
4	1 week Stimulation	
5	2 week Stimulation	
6	3 week Stimulation call	
7	4 week Stimulation	
8	5 week Stimulation call	
9	6 week Stimulation	
10	7 week Stimulation call	
11	8 week Stimulation	
12	1 week post treatment call	
13	3 month follow-up	
Group #1 Follow Up:		
14	6 months follow-up	[redacted]

15	9 months follow-up	[redacted]
16	12 month follow-up	
Group #2 Crossover/Follow Up:		
C1	Crossover lead placement (SOCT)	[redacted]
C2	2 week Stimulation	[redacted]
C3	4 week Stimulation	
C4	8 week Stimulation	
C5	3 month follow-up call	
C6	6 month follow-up call	
C7	9 month follow-up call	
C8	12 month follow-up call	

[redacted]

7.7 Subject compensation

Individuals [redacted] will receive compensation for full participation in all study visits to cover expenses while taking part in this study. [redacted]

All Group #1 and Group #2 subjects will receive:

- [redacted] after the completion of Visit 1
- [redacted] after the completion of Visit 2 Screening
- [redacted] after the completion of Visit 2 Testing
- [redacted] after the completion of each Visit 4, 5, 7, 9, 11, and 13
- [redacted] after the completion of each Visit 6, 8, 10, and 12 phone calls

Group #1 subjects will also receive:

- [redacted] after the completion of each Visit 14-16

Group #2 subjects that crossover to receive stimulation will also receive:

- [redacted] after the completion of Visit C1 Testing
- [redacted] after the completion of each Visit C2-C4
- [redacted] after the completion of each Visit C5-C8 phone calls

If a subject volunteers to participate in an additional Visit 2 (returns for another session of stimulation testing) the subject will receive [redacted] compensation at the completion of that visit.

If a subject participates in an Unscheduled Visit (other than an additional Visit 2), they will receive [redacted] compensation for completion of that unscheduled visit.

[redacted]

8.0 Data management

8.1 Subject screening and identification logs

A subject screening log will be completed at each site for all subjects who were considered for the study. [redacted] The Subject Identification log will be completed for subjects enrolled in the study.

8.2 Data collection

For this study, an Electronic Data Capture (EDC) system which utilizes electronic CRFs (eCRFs) will be used. A 21 CFR Part 11 compliant system will be selected for use which enables entry of study data into an Electronic Data Capture system by each participating clinical site. The EDC system will be validated prior to being available for data entry at the sites and will include appropriate electronic security measures such as controlled password protected access, storage and back-up on the data on a secure HTTP (SSL) server, and appropriate data entry logic and validation checks.

Paper source documents, where applicable, will be completed and maintained in a fashion that is consistent with accepted Good Clinical Practices. If necessary, corrections to the source documentation will be made by using a single line strikeout with the initials and date of the person making the correction. The corrections will be made so as not to obscure the original data. Correction fluid or correction tape may not be used. Where specified, the Principal Investigator must sign and date the source documentation and questionnaires. All paper study documentation will be stored in a locked storage facility (either a locked office or a locked cabinet).

After subject randomization and through Visit 13, selected surveys will be administered by a study team member who will not know the randomization assignment of each subject and thus will be designated as a Blinded Evaluator.

8.3 Subject numbering

Screened and consented consecutive subjects will be given a unique study ID number. Subjects who sign consent and do not meet all study eligibility criteria will be considered screen failures and not count against the number of enrolled subjects. Subjects who are randomized will be counted as enrolled. [redacted]

8.4 Confidentiality of data

Every effort will be made to protect subject confidentiality. Subject names and personal identifiers will not appear in any publications resulting from this work. [redacted]

8.5 Data processing

SPR Therapeutics, Inc. (or their authorized representatives) will be responsible for database creation, generation of database queries, and data analysis. [redacted]

8.6 Blinding

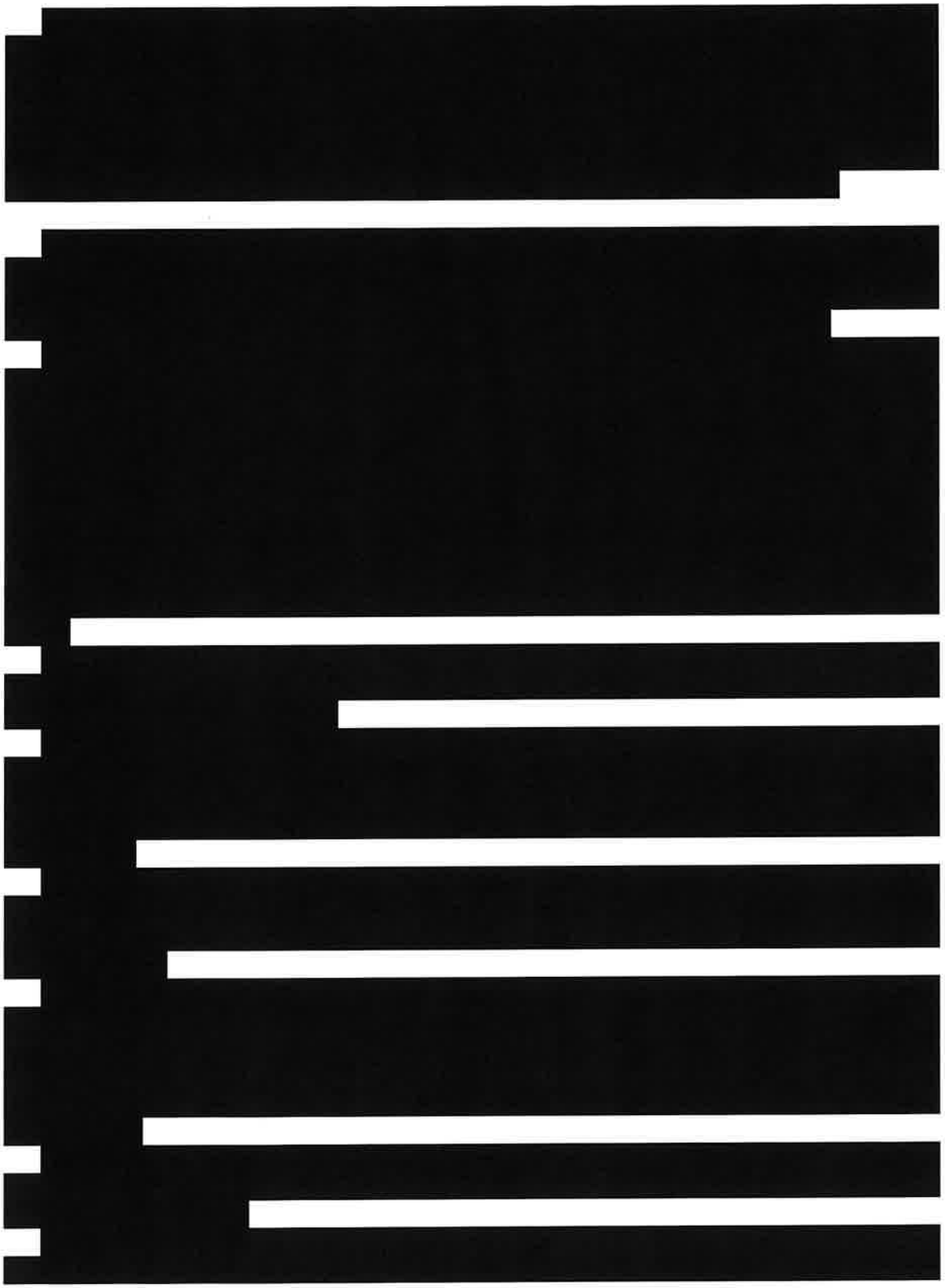
[redacted] Blinding of subjects will not be broken until the subject completes Visit 13 unless necessary for the safety of the subjects.

Each site will designate a study team member to serve as the blinded evaluator, who will not know the randomization assignment of the subjects. [redacted]

Unblinded study staff will perform all activities that cannot be performed by the blinded evaluator. [redacted]

8.7 Plan to maximize subject retention and minimize loss of data

Significant efforts will be made to maintain maximum subject retention and follow up data and minimize the percentage of missing data [redacted]



[redacted]

9.0 Study monitoring

9.1 Designation of study monitor

SPR Therapeutics or a designated qualified study monitor will monitor this study. Other appropriately qualified clinical monitors may also be involved in the monitoring of study sites.

9.2 Training

SPR Therapeutics or its representative will conduct a Site Initiation and Training Visit prior to initiation of the study. The purpose of this visit will be to develop a common understanding of the clinical protocol, CRFs, study specific procedures, Investigator Responsibilities, and Good Clinical Practices (GCPs) among the clinical research monitors and the Site team.

9.3 Routine monitoring

Monitoring visits to the Clinical Site will be conducted periodically, as determined by the rate of subject enrollment, during the study to ensure that the most currently approved version of the Protocol is being followed and that the site is in adherence with all Good Clinical Practices and any specific study Data Monitoring Plan that is in place.

[redacted]

9.4 Device accountability

[redacted]

9.5 Independent Clinical Events Reviewer

An Independent Clinical Events Reviewer (ICER) will be utilized for this study to adjudicate study related adverse events (AEs). AE information, will be provided to the ICER to assess

seriousness and/or relatedness. The ICER's adjudication will be considered the final determination. .

10.0 Adverse event reporting

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient whether or not related to the medical device or procedure. Adverse Events will not be captured unless they are study-related or the relationship is unable to be determined.

An Adverse Device Effect (ADE) is a study-related Adverse Event. Adverse Device Effects (ADEs) that occur during the study will be captured on an Adverse Event Form and reported to the Sponsor. If the relationship of the adverse event to the System is not able to be determined, it will be captured on an Adverse Event Form and reported to the Sponsor. Specific details regarding the ADE, including the event category, severity of event, and seriousness will be collected. Any necessary treatment or intervention required and the resolution status of the ADE will also be documented. ADEs will be followed to resolution. Any ADEs that meet the requirements for Medical Device Reporting (MDR) will be entered into SPR's complaint system.

All ADE's are further categorized as anticipated or unanticipated. Any ADE's specified in the Risk Analysis of this Investigational Plan will be considered "anticipated". All other ADE's are considered "unanticipated". Anticipated events that occur with a greater frequency than expected are also considered unanticipated.

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in this protocol or application or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

[redacted]

Table 6 Unanticipated Adverse Device Event Sponsor Contact Information

UNANTICIPATED ADVERSE DEVICE EVENT SPONSOR CONTACT INFORMATION			
Name/Title	**Email address**	**Telephone Number**	**Fax Number**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

It is the responsibility of the investigator to inform his Institutional Review Board (IRB) of any ADEs and UADEs as required by the IRB. In addition, some IRBs will require that AEs that are

serious in nature, even if not study-related, will be reported as well. SPR Therapeutics is responsible for furnishing the required information to the appropriate regulatory authorities.

Deficiencies related to the identity, quality, durability, reliability, usability, safety or performance of a device should be reported to SPR promptly. Sites will be provided with instructions for the reporting of device complaints in accordance with SPR's standard operating procedures.

11.0 Risk benefit analysis

The potential risks and benefits to study subjects participating in this study are listed below.

11.1 Potential benefits

Subjects in this study may not receive any direct benefit by participating in this study. [redacted]

[redacted]

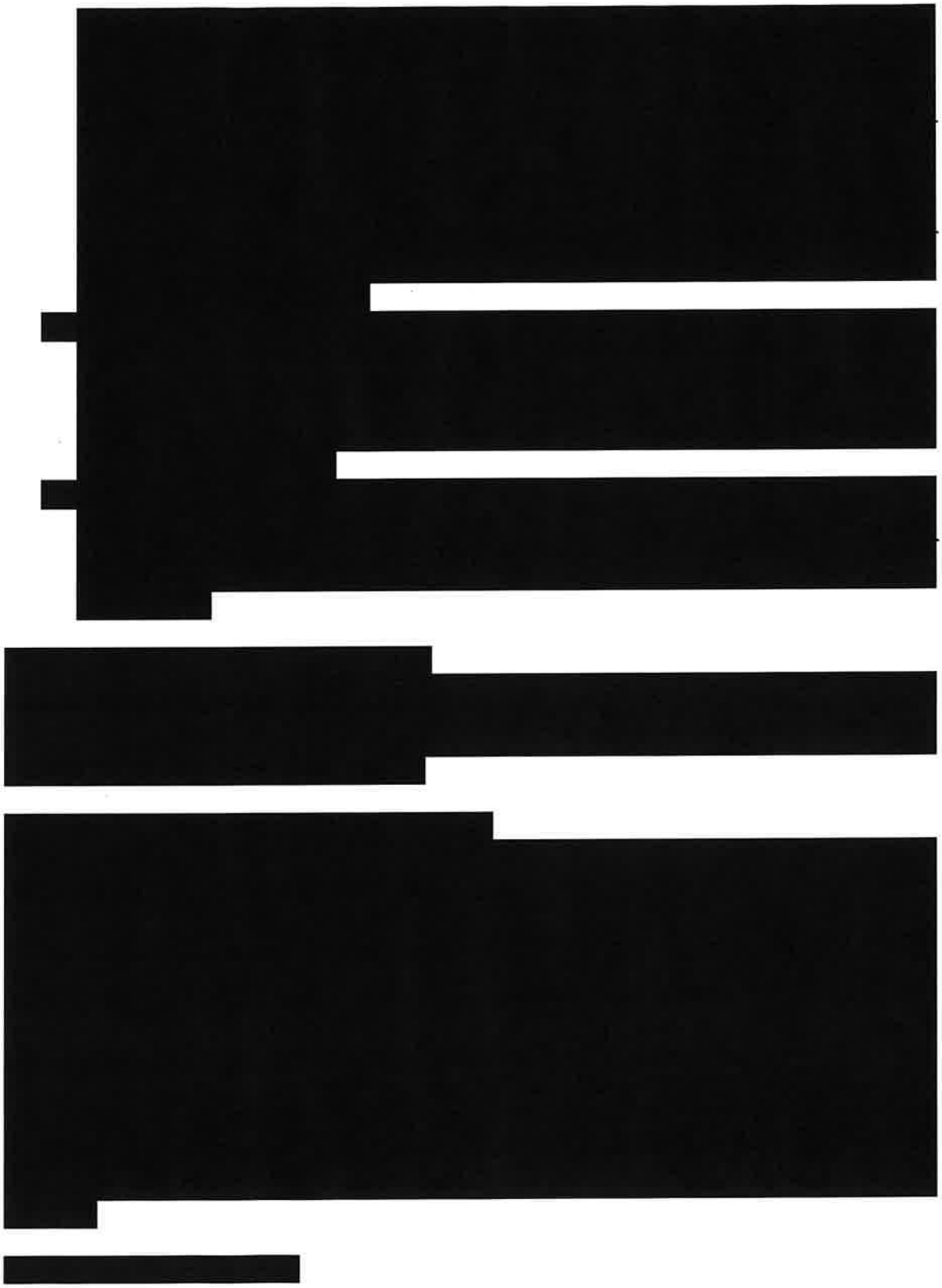
This research may benefit future patients with post-amputation pain.

11.2 Known and anticipated risks

The risks listed below are described as either common [redacted], uncommon [redacted] or rare [redacted]

[redacted]

[redacted]



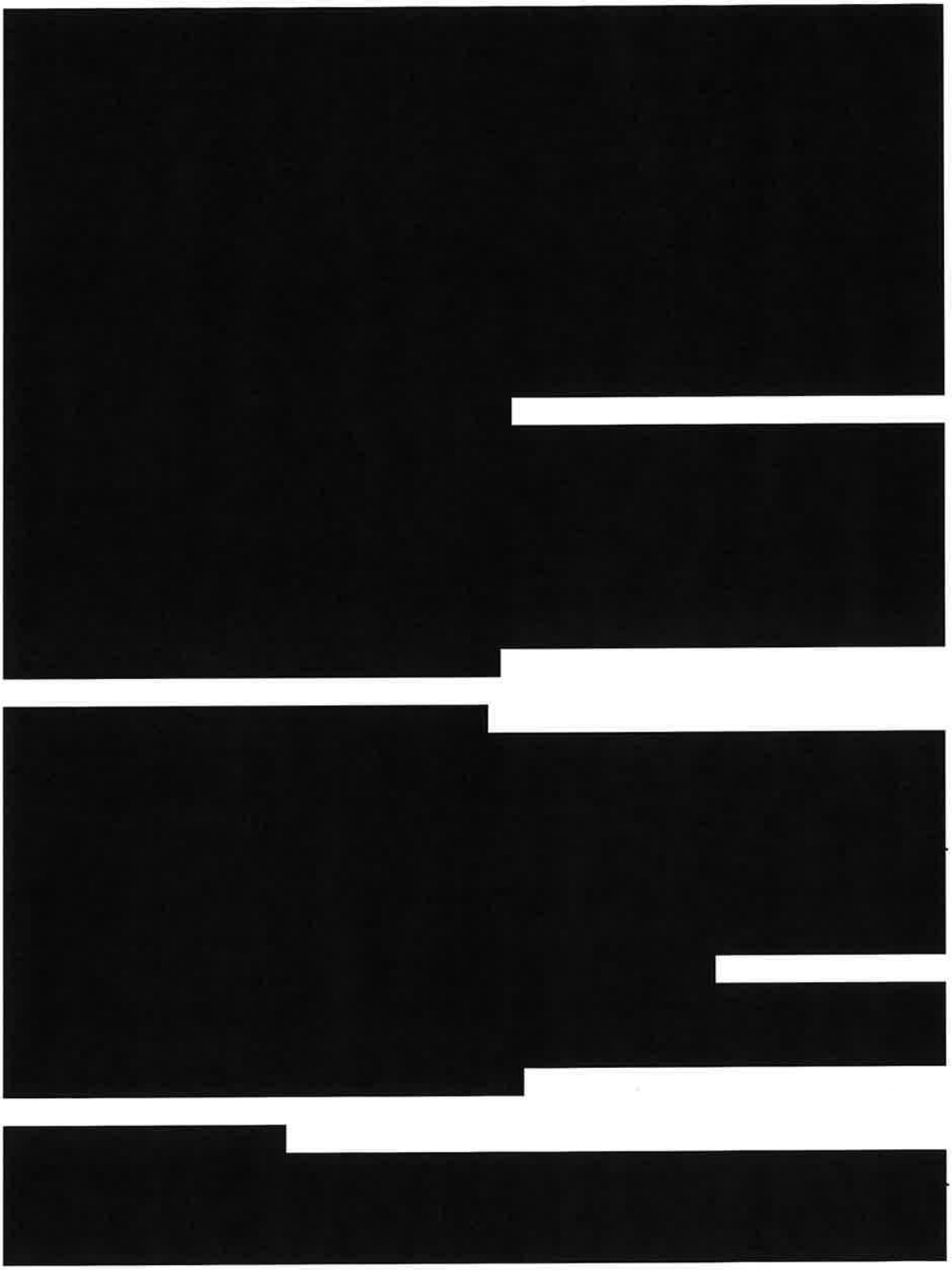
[redacted]

[redacted] **Risk of skin irritation, infection, or inflammation at the lead exit site**

[redacted]

[redacted] **Risk of the percutaneous lead breaking beneath the skin**

[redacted]



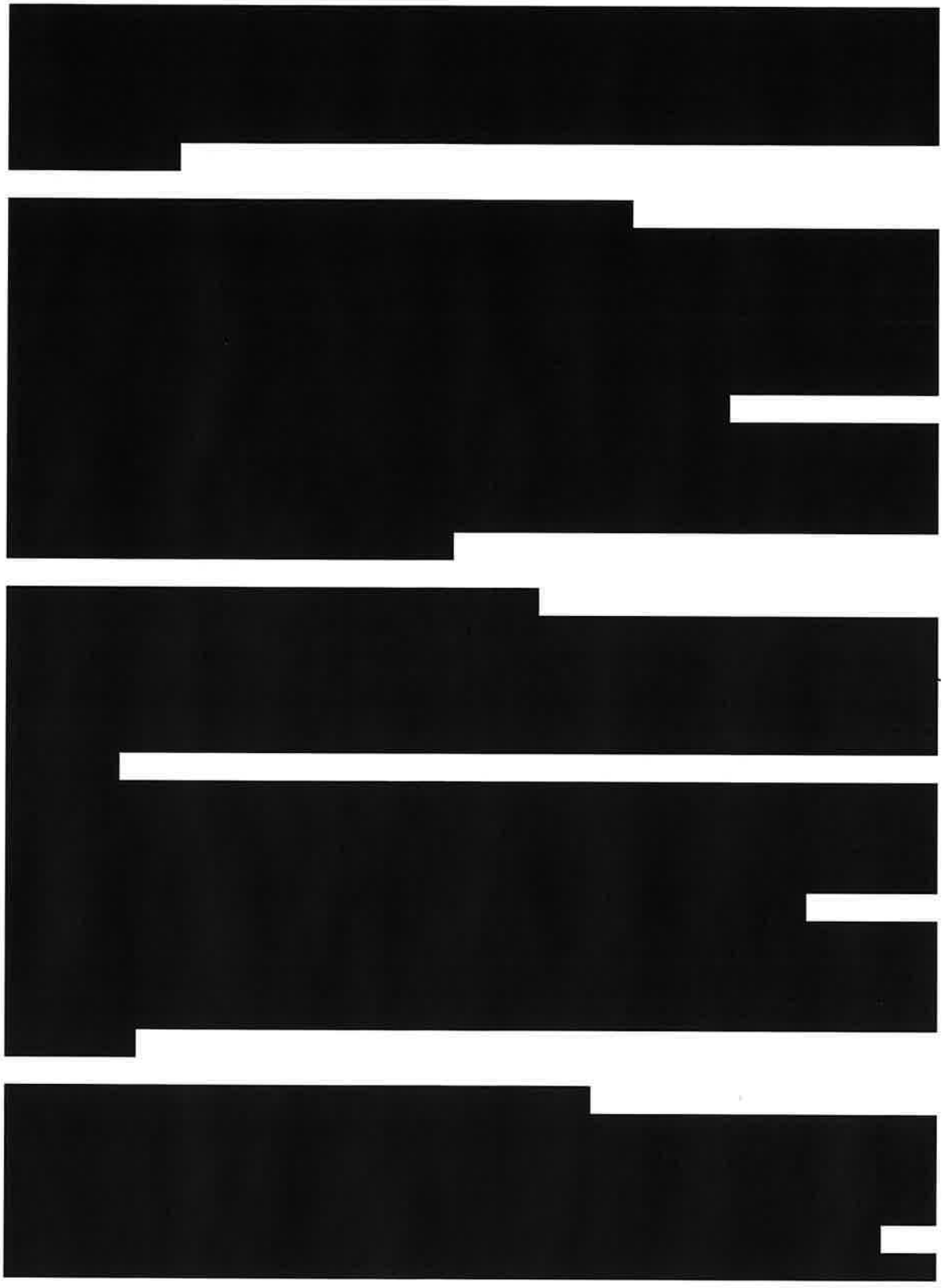
[redacted]

[redacted] **Risk of skin irritation under the pad, lead connector tape, or bandages**

[redacted]

[redacted] **Risk of discomfort or increased pain**

[redacted]



[redacted]

[redacted]

[redacted]

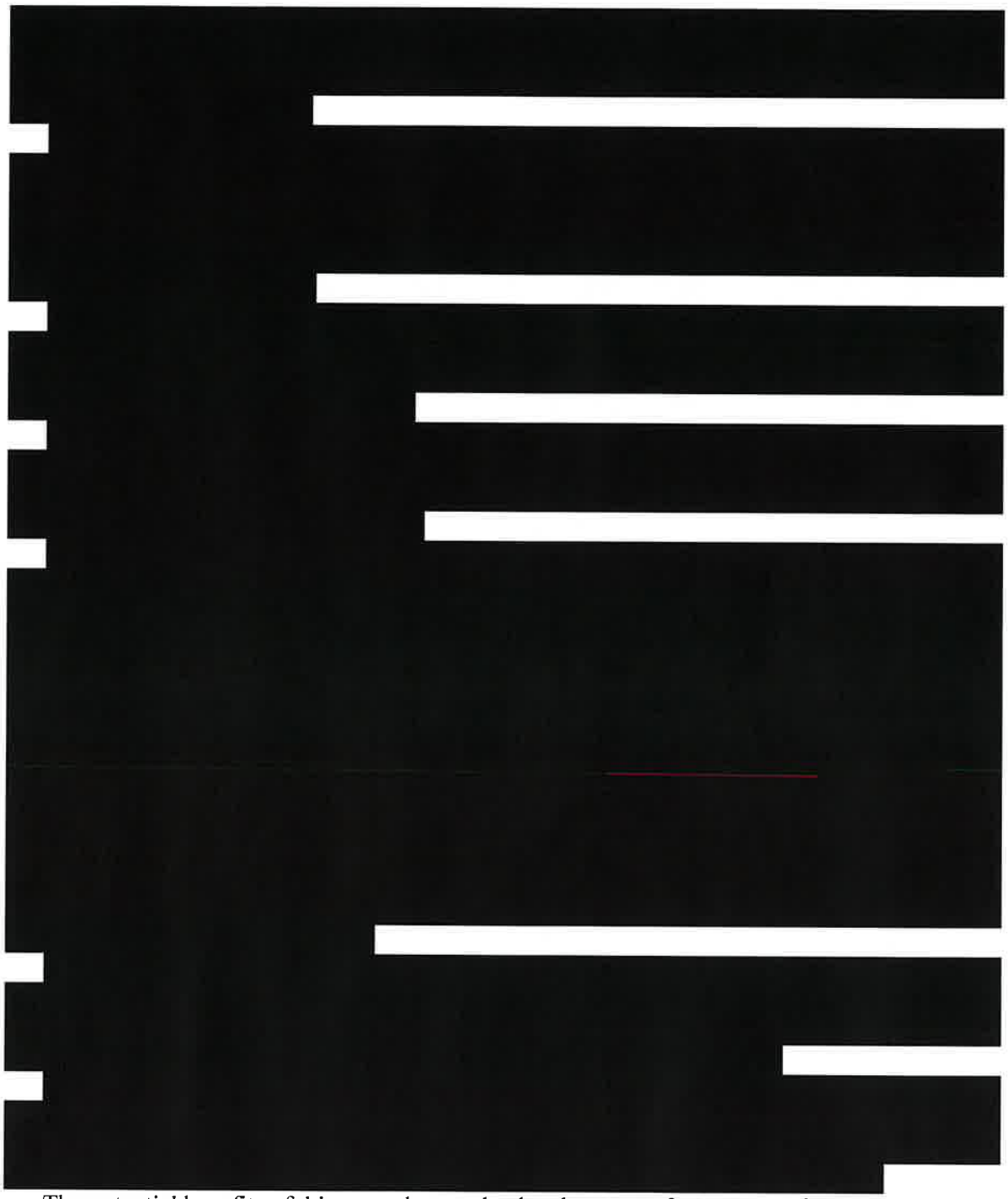
11.3 Risk analysis

As described above, all efforts will be made to mitigate each potential risk associated with the use of the system. [redacted]

The potential risks of participation in this study have been minimized such that they are unlikely to occur. [redacted]

11.4 Risk justification: the proposed study presents a justifiable risk to the subjects

[redacted]



The potential benefits of this procedure to the development of a treatment for post-amputation pain outweigh the risks associated with this procedure and temporary treatment.

12.0 Ethical considerations

12.1 Ethical Standard

The study will be performed in accordance with applicable FDA regulations, relevant parts of the ICH Guidelines for Good Clinical Practices (GCPs), and the Declaration of Helsinki. The study will not begin enrollment until regulatory approval has been received from the relevant regulatory bodies.

12.2 Institutional review boards

It is the responsibility of the Principal Investigator to obtain and maintain written approval of the study protocol and the informed consent from the appropriate Institutional Review Board (IRB). It is further the Principal Investigator's responsibility to notify the IRB regarding any amendments/supplements to either the study protocol or the consent form. A copy of the written IRB approval, along with the approved versions of the consent and protocol, will be maintained in the study regulatory file. Written approvals will identify the study name and document the date of review.

12.3 Informed consent form

In accordance with 21 CFR 50, it is the responsibility of the Principal Investigator to give each participant (or the participant's legally authorized representative) full and adequate verbal and written information about the objectives of the study, the study procedures, and the potential risks of participating in the study prior to inclusion in the study. Potential study participants will be informed that their participation is voluntary and that they may withdraw their consent at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled. Potential participants will also be informed that withdrawal from the study will not jeopardize their future medical care. [redacted]

It is the Principal Investigator's responsibility to obtain a signed Informed Consent Form from each potential study participant prior to performing any study-related procedures and to document the informed consent process in the subject record.

The Informed Consent Form will be amended whenever new information becomes available that may be relevant to the subjects continued participation. [redacted]

12.4 Amending the protocol

This study will be carried out in accordance with this Study Protocol. SPR Therapeutics will prepare written amendments to revise the protocol, if necessary. Changes that are deemed administrative in nature, which do not require IRB approval (such as editorial changes for clarity or changes to contact information) may be made without any further approvals. Documentation of the approval of the amendment will be maintained in the study regulatory files.

13.0 Study administration

13.1 Record retention

The Investigator agrees to retain study-related documents in a secure location to which access can only be gained if required. Following study completion, the following documents will be archived: the study regulatory files containing all Good Clinical Practice (GCP) documents, including signed Informed Consent forms, patient-related materials, and CRFs.

13.2 Criteria for terminating the study

SPR Therapeutics reserves the right to terminate the study at any time. SPR Therapeutics only intends to exercise this right for valid scientific or administrative reasons, and reasons related to the protection of Human Subjects participating in this study. [redacted]

13.3 Criteria for terminating a center

The Sponsor reserves the right to suspend or stop the enrollment of subjects at a study center at any time after the study initiation if no subjects have been enrolled or if enrollment numbers are well below anticipated enrollment expectations. [redacted]

13.4 Investigator qualifications, responsibilities, and training

To participate in this study, the Investigator must sign the Investigator Agreement which documents his responsibilities in the study. The Investigator will require training on this study plan and the device. [redacted]

[redacted]

[redacted]

GENERAL

SURVEYS

PROCEDURES