

Official Title:

A Randomized, Double-Blinded, Placebo-Controlled, Multicenter Pilot Study of the SPRINT™ Peripheral Nerve Stimulation (PNS) System for the Treatment of Post-Amputation Pain

NCT#: NCT01996254

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A Randomized, Double-Blinded, Placebo-Controlled, Multicenter Pilot Study of  
the SPRINT™ Peripheral Nerve Stimulation (PNS) System for the Treatment of  
Post-Amputation Pain

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June 20, 2016  
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**CONFIDENTIAL INFORMATION**

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

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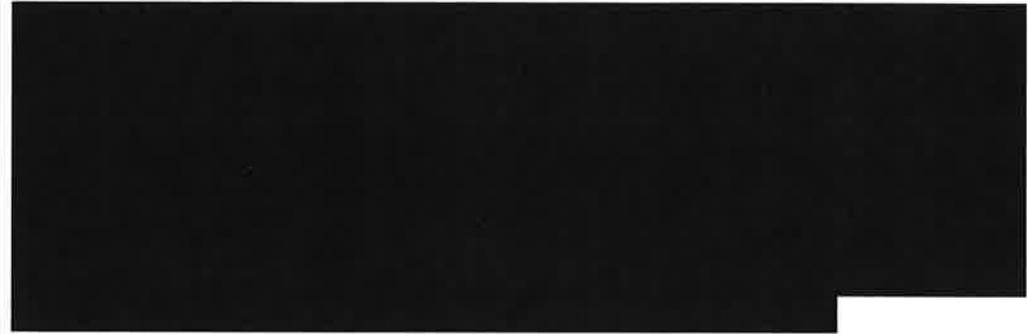


1.0 Protocol Synopsis

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| <p><b>Title</b></p>                         | <p>A Randomized, Double-Blinded, Placebo-Controlled, Multicenter Pilot Study of the SPRINT™ Peripheral Nerve Stimulation (PNS) System for the Treatment of Post-Amputation Pain</p>  |
| <p><b>Indication</b></p>                    | <p>The SPRINT Peripheral Nerve Stimulation (PNS) System is indicated for use for up to 60 days for [REDACTED] pain.</p>  |
| <p><b>Investigational (Test) Device</b></p> | <p>The SPRINT Peripheral Nerve Stimulation (PNS) System: [REDACTED]</p>  |
| <p><b>Study Design</b></p>                  | <p>Prospective Randomized, Double-Blinded, Placebo-Controlled, Multicenter Pilot Study to demonstrate superiority of the investigational treatment over the control treatment.</p>   |
| <p><b>Study Objective</b></p>               | <p>The study objective is to gather data regarding the safety and effectiveness of the SPRINT PNS System for the treatment of post-amputation pain: [REDACTED] [REDACTED] The study will determine if the treatment specific effect of the investigational treatment is significant and different than the placebo effect.</p>   |
| <p><b>Study Plan</b></p>                    | <p><b><u>Amputees must have an average pain [REDACTED] to qualify</u></b><br/>         Individuals with one or more lower extremity amputations reporting [REDACTED] pain [REDACTED] on the Brief Pain Inventory Short Form (BPI-SF [REDACTED]) 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 [REDACTED] baseline diary to record their [REDACTED] post-amputation pain [REDACTED] for each amputated limb. Individuals must report [REDACTED] to qualify.</p> <p><b><u>Percutaneous leads will be placed in the upper leg adjacent to the femoral and/or sciatic nerves</u></b><br/>         Qualifying subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control). In all subjects, leads will be placed percutaneously [REDACTED] [REDACTED] All subjects will be instructed to use the SPRINT Stimulator(s) continuously each day [REDACTED] during the [REDACTED] home trial. Initially, subjects will use the stimulation system [REDACTED]: in Group #1, the system will deliver electrical stimulation [REDACTED], while in Group #2, the system will deliver sham (placebo) stimulation. [REDACTED], <b><u>Group #2 will begin receiving the investigative treatment</u></b></p> |

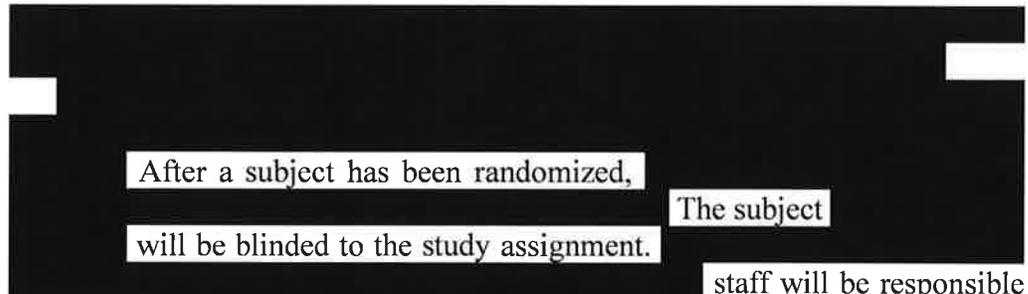


Following the initial [REDACTED] home trial, subjects will continue using the stimulation system [REDACTED]. While Group #1 will continue receiving actual stimulation, Group #2 will begin receiving actual stimulation [REDACTED]. At the end of the home trial, subjects will return to the clinic to have their lead(s) removed. After lead removal, the subjects will be followed for 12 months.



**Daily medications affecting pain will be permitted at levels established during baseline and PRN (pro re nata) medications will be permitted as needed**

All subjects will be permitted to continue use of all medications affecting pain throughout the study; however, dosages of these medications will be controlled during the study. Subjects will be permitted to reduce or maintain their dosages of medications affecting pain but will be asked not to increase their dosages of these medications above the established baseline dosages documented at baseline. To be eligible for lead placement, individuals cannot have added any new medications affecting pain, including as-needed (PRN) medications, [REDACTED] prior to initiating the baseline diary (based upon the subject-reported medication history). Consistent with clinical practice, all subjects will be permitted to continue to use PRN medications throughout the study.



After a subject has been randomized,

The subject

will be blinded to the study assignment.

[REDACTED] staff will be responsible for actions [REDACTED] such as lead placement, adjusting stimulation parameters, changing bandages, assessing the lead exit sites, and responding to questions from the subjects.

**Number of Sites**

Up to 10 investigational sites will be initiated.

**Number of Subjects**

Up to 54 individuals will be enrolled. Using a 1:1 randomization scheme, subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control).



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| <p><b>Inclusion Criteria</b><br/><i>(assessed at Eligibility Visit 1)</i></p>                | <ul style="list-style-type: none"> <li>• At least 18 years old</li> <li>• Traumatic lower extremity amputation(s)</li> <li>• Healed amputation and healthy residual limb based upon the investigator's evaluation</li> <li>• Post-amputation pain [REDACTED] despite receiving at least two conservative therapies</li> <li>• Able to understand and willing to take part in study and comply with all study requirements</li> </ul>  |
| <p><b>Additional Inclusion Criteria</b><br/><i>(assessed prior to the Testing Visit)</i></p> | <ul style="list-style-type: none"> <li>• Average post-amputation pain [REDACTED]</li> </ul>   |
| <p><b>Exclusion Criteria</b></p>   | <ul style="list-style-type: none"> <li>• Change of prescribed medications affecting pain [REDACTED] as indicated from subject-reported medication history.</li> <li>• Beck Depression Inventory (BDI-II) score of &gt; 20</li> <li>• Compromised immune system based on medical history [REDACTED]</li> <li>• Diabetes Mellitus Types I or II from medical history or subject reported history</li> <li>• Implanted spinal cord stimulator, cardiac pacemaker/defibrillator or Deep Brain Stimulator</li> <li>• History of bleeding disorder [REDACTED]</li> <li>• History of valvular heart disease</li> <li>• Confounding central nervous system injuries and disorders [REDACTED]</li> <li>• Allergy to all local anesthetic agents [REDACTED]</li> <li>• Allergy to skin-contact materials [REDACTED]</li> <li>• History of recurrent skin infections</li> <li>• Botulinum toxin injection within the last three months in the affected limb</li> <li>• Steroid injection within the last six weeks in the affected limb</li> <li>• Subject has participated in any drug or device trial in the past 30 days</li> <li>• Subject has participated in previous [REDACTED] Amputee Pain feasibility trial</li> <li>• Any other condition that may interfere with the ability to participate in a clinical trial [REDACTED] as determined by the Investigator</li> <li>• Prisoners</li> </ul> |



|   |   |
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| <b>Additional Exclusion Criteria (verified after initial criteria verification)</b> | <ul style="list-style-type: none"> <li>• INR &gt; 1.5 for those on warfarin</li> <li>• Pregnant [REDACTED]</li> </ul>   |
| <b>Primary Safety Endpoint</b>  | <ul style="list-style-type: none"> <li>• Occurrence of device-related and procedure-related adverse event rates. Adverse events will be assessed at all visits.</li> </ul>  |
| <b>Primary Clinical Endpoint</b>  | <p>Pain Intensity: [REDACTED] post-amputation pain [REDACTED] that have intensities [REDACTED] during the baseline period and receive treatment with an investigational device will be used to assess the primary efficacy endpoint. All amputees will record [REDACTED] daily post-amputation pain scores [REDACTED] diaries using [REDACTED]. For each individual, [REDACTED] post-amputation pain [REDACTED] during baseline in a leg that receives blinded treatment from an investigational device(s) will qualify to be used in the determination of clinically-meaningful success for that subject throughout the study. Each amputee must have [REDACTED] reduction [REDACTED] to be considered a success in the primary effectiveness endpoint analysis.</p> <p>The primary endpoint of the study compares the proportion of subjects in Group #1 relative to that in Group #2 that achieve [REDACTED] reduction in [REDACTED] post-amputation pain from baseline to the end [REDACTED] of the home trial, examining the statistical superiority of proportion of clinical successes of Group #1 over the proportion of successes of Group #2. The post-amputation pain intensity scores will be determined for each subject by taking the mean of the daily average pain intensity [REDACTED] reported in the [REDACTED] diary at baseline compared to the mean score for the same region(s) of pain reported [REDACTED].</p> |
| <b>Secondary Endpoints</b>  | <p>[REDACTED] Durability of the treatment effect for average pain intensity [REDACTED]</p> <p>[REDACTED] Durability of the treatment effect for average pain intensity [REDACTED]</p> <p>The following secondary outcomes will be measured [REDACTED]</p> <ul style="list-style-type: none"> <li>• Pain interference [REDACTED]</li> <li>• Pain disability (Pain Disability Index)</li> <li>• Depression (BDI-II)</li> <li>• Analgesic usage</li> <li>• Prosthetic usage [REDACTED]</li> <li>• Subject Satisfaction Survey</li> </ul>   |
| <b>Exploratory Analyses</b>   | <ul style="list-style-type: none"> <li>• Treatment effect in Group #2</li> <li>• Global impression of change (Patient Global Impression of Change)</li> <li>• Analyses of changes in average RLP [REDACTED]</li> </ul>  |



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|--|--|
|  | <ul style="list-style-type: none"><li>• Analyses of changes in average PLP [REDACTED]</li><li>• Analyses of changes in worst RLP [REDACTED]</li><li>• Analyses of changes in worst PLP [REDACTED]</li><li>• Non-opioid medication use</li><li>• Pain Catastrophizing Scale (PCS)</li><li>• Clinician Satisfaction Survey</li></ul> |
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## 2.0 General Information

### 2.1 Title of Investigation

A Randomized, Double-Blinded, Placebo-Controlled, Multicenter Pilot Study of the SPRINT® Peripheral Nerve Stimulation (PNS) System for the Treatment of Post-Amputation Pain

### 2.2 Sponsor Name and Address

SPR Therapeutics, Inc.  
22901 Millcreek Boulevard, Suite 110  
Cleveland, OH 44122  
Phone: 216-378-9108  
Fax: 216-378-9116

And:

SPR Therapeutics, Inc.  
308 West Rosemary Street, Suite 308  
Chapel Hill, NC 27516  
Phone: 919-928-8005  
Fax: 919-928-8006

### 2.3 Name of the Investigational Device

SPRINT® Peripheral Nerve Stimulation (PNS) System

### 2.4 Study Objective

The study objective is to conduct a pilot study to gather data regarding the safety and effectiveness of the SPRINT PNS System for the treatment of post-amputation pain: [REDACTED]

[REDACTED] Presently available treatment options for the reduction of post-amputation pain are associated with lack of efficacy or technical barriers. Prior investigations suggest that peripheral nerve stimulation (PNS) has the potential to be a safe and effective treatment option for peripheral pain. A less invasive approach using peripheral leads rather than the leads used in spinal cord stimulation may be more acceptable to patients and the clinicians implementing these systems.

To date [REDACTED] subjects have been enrolled in a previous version of this study, which served as a feasibility study. This initial study demonstrated the clinical and technical feasibility of electrically stimulating peripheral nerves [REDACTED] reduce post-amputation pain. The proposed study will [REDACTED] gather additional data on the safety and effectiveness of our approach, including assessment of a placebo effect. The results of the [REDACTED] study will be used by the Sponsor, SPR Therapeutics, [REDACTED]

### 2.5 Funding

The proposed study is funded by the Sponsor, SPR Therapeutics, and [REDACTED]

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SPR Therapeutics, Inc.

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[REDACTED]

### 3.0 Introduction and background

#### 3.1 Introduction

*Many amputees suffer from post-amputation 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<sup>1</sup>. The post-amputation pain 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<sup>2-4</sup>. Amputees may experience two types of post-amputation pain: [REDACTED]

[REDACTED] Post-amputation pain [REDACTED] can have a significant effect on quality of life. 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.

*Electrical stimulation can treat post-amputation pain, but existing methods are too cumbersome, complex, or invasive, which limits their use in clinical practice*

Electrical stimulation can be an effective method for treating post-amputation pain, but present 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 treatment compliance. Implanted spinal cord stimulation (SCS) systems involve invasive lead implantation in the spinal column. SCS systems often have problems of lead migration, resulting in either the need for frequent reprogramming or clinical failure. A minimally-invasive implanted system with a lead that is placed percutaneously [REDACTED] would provide a desirable alternative to current approaches.

Published studies indicate that peripheral nerve stimulation can be very effective in treating many types of neuropathic pain, including post-amputation pain<sup>5-12</sup>. 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<sup>5, 8, 13</sup>.

In a series of case studies, peripheral nerve stimulation [REDACTED] 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<sup>5-7, 9, 10</sup>. Thus, the major limitation of existing methods of peripheral nerve stimulation (PNS) is the need for a simple method of placing electrode leads [REDACTED].

*Our previous feasibility study suggests a simple percutaneous method of placing leads can reduce pain [REDACTED]*

We propose to address the limitations of existing methods with a percutaneous method [REDACTED]

[REDACTED]

[REDACTED]

***The present study will determine if our approach of percutaneously stimulating the nerves [REDACTED] will produce greater pain relief than the placebo effect***

The Sponsor, SPR Therapeutics, proposes to gather data on the safety and clinical effectiveness of electrically stimulating peripheral nerves to reduce post-amputation pain. This evaluation is a randomized, double-blinded, placebo-controlled, multicenter pilot study of the SPRINT Peripheral Nerve Stimulation (PNS) System for the treatment of post-amputation pain. The device consists of a [REDACTED] lead that delivers electrical stimulation [REDACTED]

[REDACTED]

In all subjects, leads will be placed percutaneously [REDACTED]

Initially, subjects will use the stimulation system [REDACTED] in Group #1, the system will deliver electrical stimulation [REDACTED], while in Group #2, the system will deliver sham (placebo) stimulation. This study will determine if the specific effect of the investigative treatment is [REDACTED] different than the placebo (sham) effect.

Following the [REDACTED] home trial, subjects will continue using the stimulation system [REDACTED]. While Group #1 will continue receiving actual stimulation, Group #2 will begin receiving actual stimulation as well [REDACTED].

All subjects will be instructed to use the SPRINT Stimulator(s) [REDACTED]. At the end of the home trial, subjects will return to the clinic to have their lead(s) removed. After lead removal, the subjects will be followed [REDACTED].

**3.2 Background**

A discussion of the currently available treatment options for the treatment of post-amputation pain are presented below.

***Post-amputation pain is a significant problem that is not adequately addressed by present treatment options***

Amputation results in chronic pain in many patients and up to 70%-80% of patients have significant post-amputation pain [REDACTED]

[REDACTED]

[REDACTED]

██████████ Post-amputation 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██████████.

***Post-amputation 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██████████. The severity and high incidence of post-amputation pain make it a significant medical problem██████████. The pain often leads to discouragement, anger, embitterment, and general suffering<sup>21</sup>. Post-amputation pain frequently causes further disability and greatly reduces the quality of life for amputees██████████. 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██████████. In amputees with moderate to severe post-amputation 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██████████.

***Present methods of medication, injections, physical modalities, psychological strategies, and surgery are unsatisfactory in managing post-amputation pain***

Many techniques have been developed to treat post-amputation pain, but none of them are consistently successful and all of them are ultimately insufficient██████████ (Table 1). Presently, most patients are managed with medications, but approximately a third of amputees still report severe post-amputation 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 post-amputation pain and are rarely sufficient in managing moderate to severe chronic post-amputation pain██████████.

The use of opioid analgesics has shown limited success in a few trials, but the data are limited and few amputees achieve consistent long-term pain relief from opioids██████████. 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██████████.

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 post-amputation pain██████████. In small trials, some benefit has been seen with administering dextromethorphan or calcitonin██████████, but the correct dosage has not yet been determined and there have been few supporting trials to demonstrate efficacy with these medications██████████.

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

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 [REDACTED].

Psychological strategies, such as biofeedback and psychotherapy, may be used as an adjunct to other therapies but are seldom sufficient, not specific to post-amputation pain, and there are few studies demonstrating their efficacy [REDACTED]. 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 [REDACTED].

Many surgical procedures have been attempted, but few are successful and many are contraindicated for the majority of the amputee patients [REDACTED]. Because neuromas (a tangled mass of sensitive nerve endings) are implicated with post-amputation pain, there have been numerous attempts to remove them surgically, but generally a neuroma develops when a nerve is cut and the pain relief only lasts for the few weeks that it takes for a new neuroma to form [REDACTED]. 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 [REDACTED]. Thus, present medical treatments of post-amputation pain are inadequate, and many sufferers resort to living with pain that is poorly controlled with medications.

|            |            |            |            |            |            |            |
|------------|------------|------------|------------|------------|------------|------------|
| [REDACTED] |
| [REDACTED] |
| [REDACTED] |
| [REDACTED] |

### 3.2.1 Neurostimulation can reduce post-amputation pain but present methods require a complex surgical approach or have other practical limitations

#### *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. [REDACTED]

[REDACTED] 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 [REDACTED]. Most patients ultimately decide to discontinue use of the system [REDACTED].

***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 and 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 [REDACTED] confirms that the location of the electrode [REDACTED] should be sufficient to provide pain relief. Pain relief can be excellent initially, but maintaining long-term [REDACTED] coverage is often a problem as the lead migrates within the epidural space [REDACTED].

Lead migration is a common complication for spinal cord stimulators occurring in up to 10-35% of the cases [REDACTED]. When the lead migrates, the active contact moves farther from the target fibers [REDACTED]. 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<sup>11</sup>, and up to 88% of patients may require one or more reprogramming visits after initial implantation<sup>48</sup>. 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<sup>48</sup>. The option of reprogramming the contacts has improved the chances of regaining some pain relief, but it is often difficult to regain [REDACTED] 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<sup>48-51, 53, 54</sup>. 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 [REDACTED]. Lead migration [REDACTED] loss of pain relief with SCS, [REDACTED]

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 [REDACTED].

***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 [REDACTED]. 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 [REDACTED]. Due to cost and invasiveness, it is unlikely that either MCS or DBS will be recommended for post-amputation pain until additional clinical trials are performed to refine the patient selection criteria and confirm the long term effectiveness [REDACTED].



[REDACTED]

|            |            |            |            |
|------------|------------|------------|------------|
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |
| [REDACTED] | [REDACTED] | [REDACTED] | [REDACTED] |

***Electroconvulsive therapy is rarely used to treat post-amputation pain***

There have been very limited reports on the use of electroconvulsive therapy (ECT) in the treatment of post-amputation pain. 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 with post-amputation pain [REDACTED].

***High (> 1 kHz) frequency nerve block 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) nerve block has been shown to decrease transmission of peripheral nerve signals, and case studies suggest it may reduce post-amputation pain, but it would require an invasive surgery to implant the electrodes around the nerve and it may be difficult to maintain sufficient nerve block in practice in ambulatory patients chronically in their home environment [REDACTED]. Additionally, blocking 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 nerve block is unlikely to be more effective in relieving post-amputation 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 post-amputation pain [REDACTED].

**3.2.2 Post-amputation pain 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***

[REDACTED] Peripheral nerve stimulation (PNS) has been shown to provide dramatic pain relief, improve sleep, increase quality of life, allow [REDACTED] patients to return to work, and reduce or eliminate dependence on opioid analgesia [REDACTED].

PNS is regarded as very effective in treating many types of neuropathic pain, including post-amputation pain [REDACTED].

[REDACTED]

Though PNS has a high success [REDACTED] 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 [REDACTED].

[REDACTED]

### 3.2.3 Summary of feasibility study

*The previous feasibility study demonstrated that the proposed method of PNS can provide substantial relief of post-amputation pain*

[REDACTED]

*Data collected during the case-series home trial demonstrated pain relief and improvements in quality of life could be sustained*

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

*In addition to reductions in pain, significant improvements in quality of life were reported*

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] *confirms the individual has the potential to receive pain relief from stimulation*

[REDACTED]

*Subjects* [REDACTED] *which can be an additional source of post-amputation pain*

[REDACTED]

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 [REDACTED]. Neuromas may generate spontaneous activity [REDACTED], and the level of activity in afferent fibers innervating the region of pain has been linked to the level of post-amputation pain [REDACTED]. 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 [REDACTED]. Injection of gallamine, which increases neuroma activity, increases pain, and injection of lidocaine, which decreases neuroma activity, decreases pain in amputees [REDACTED].

[REDACTED]

[REDACTED]

[REDACTED]

### 3.3 Summary

Present treatments for post-amputation pain are inadequate for many amputee patients and are associated with a lack of efficacy. [REDACTED]

[REDACTED]

The [REDACTED] study will use the proposed randomized placebo-controlled trial design to determine if the proposed method of percutaneous PNS can provide pain relief in Group #1 (Treatment) that is significantly greater than the placebo effect observed in Group #2 (Control). [REDACTED]

## 4.0 STUDY ENDPOINTS

### 4.1 Overview

Outcome measures will be administered to each subject 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

- Post-amputation pain [REDACTED]
  - Prosthetic usage
  - Medication affecting pain
2. Brief Pain Inventory, Short Form (BPI-SF)
  3. Pain Disability Index (PDI)
  4. Beck Depression Inventory, Second Edition (BDI-II)
  5. Patient Global Impression of Change (PGIC)
  6. Pain Catastrophizing Scale (PCS)

#### 4.2 The primary efficacy endpoint will be average pain intensity

The primary efficacy endpoint will be average post-amputation pain at the end of the [REDACTED] [REDACTED] trial (in both Treatment and Control groups) compared to baseline in all qualifying regions of post-amputation pain [REDACTED]. All amputees will record post-amputation pain scores [REDACTED] for [REDACTED] amputated leg [REDACTED].

[REDACTED] Each post-amputation pain region with [REDACTED] that receives an investigational device(s) will qualify to be used in the primary outcome analysis for that subject. [REDACTED]

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 device related adverse events (AEs). All AEs that occur during the study will be documented and analyzed. Specific details regarding any observed AE will be collected on an AE Form and will be followed to resolution. The investigator will determine the severity of each AE as well as its relationship to the device and procedure. In addition, each AE will be categorized as either serious or non-serious. Any necessary treatment or intervention required and the resolution status of the adverse event will also be documented. AEs will be tabulated and summarized at the conclusion of study. [REDACTED]

Additional details on the monitoring and adjudication of AEs is described in the section regarding monitoring.

#### 4.4 Secondary Efficacy Endpoints

Several secondary endpoints are being collected to gain a better understanding of what effect, if any, the interventions will have on each measure. We intend to evaluate these endpoints

(described below) to [REDACTED]. Refer to Section 9.3 for a detailed description of each endpoint. Changes from baseline will be evaluated as secondary efficacy endpoints for the following outcome measures:

- Durability of the treatment effect on average pain intensity [REDACTED]
- Durability of the treatment effect on average pain intensity [REDACTED]
- Pain interference (BPI-SF Question #9) [REDACTED]
- Pain disability (Pain Disability Index (PDI)) [REDACTED]
- Depression (Beck Depression Inventory (BDI-II)) [REDACTED]
- Analgesic usage [REDACTED]
- Prosthetic usage [REDACTED]
- Subject Satisfaction Survey

#### 4.5 Exploratory Analyses

Additional analysis will be conducted including:

- Treatment effect in Group #2 [REDACTED]
- Global impression of change (Patient Global Impression of Change (PGIC)) [REDACTED]
- Analyses of changes in average RLP [REDACTED]
- Analyses of changes in average PLP [REDACTED]
- Analyses of changes in worst RLP [REDACTED]
- Analyses of changes in worst PLP [REDACTED]
- Non-opioid medication use [REDACTED]
- Pain Catastrophizing Scale (PCS) [REDACTED]
- Clinician Satisfaction Survey

#### 5.0 Investigational Device Description

##### 5.1 Overview

This study utilizes the SPRINT PNS System. [REDACTED]

5.2

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

**6.0 Scope**

**6.1 Number of sites**

Multi-center Study [REDACTED]

**6.2 Number of subjects**

[REDACTED]

Up to 54 individuals will be enrolled as subjects and randomized to either Group #1 or Group #2 using a 1:1 randomization scheme. A total of up to 54 subjects (27 subjects per group) will undergo lead placement. [REDACTED]

### 6.3 Study duration

The duration of this study is expected to be approximately 2 years. [REDACTED]

## 7.0 Study protocol

### 7.1 Overview

This study is a randomized, double-blinded, placebo-controlled, multicenter pilot study to evaluate the safety and effectiveness of the SPRINT peripheral nerve stimulation (PNS) system for the treatment of post-amputation pain.

### 7.2 Study population

Subjects with post-amputation pain will be recruited by the investigators, following all HIPAA guidelines, to ascertain their level of interest and willingness to take part in this project. Recruitment materials will be provided to aid in subject enrollment. [REDACTED]

[REDACTED] All recruitment materials will be IRB approved prior to their use.

### 7.3 Concurrent medications and non-drug therapies

All interventions targeting pain control will be recorded in the Case Report Form (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. Subjects will be permitted to reduce or maintain their dosages of medications affecting pain but will be asked not to increase their routine dosages of these medications above the baseline dosages that were established prior to lead placement. To be eligible for participation in the study, individuals will be required to have not added new medications affecting pain [REDACTED] prior to initiating the baseline diary according to subject reported medication history.

#### ***PRN medications will be permitted***

In addition to the medications taken regularly each day, subjects will be permitted to continue to use PRN pain medications as needed. Subjects who are not using opioids during baseline will be permitted to use any non-opioid medications as prescribed by their physician in addition to over-the-counter medications (e.g., acetaminophen, ibuprofen, etc.) as PRN medications affecting

pain as needed. Subjects who are using opioids during baseline will also be permitted to increase their use of their existing opioid as prescribed by the investigator.

Subjects will also be permitted to use over-the-counter medications as needed for pain (e.g., headache or back pain) unrelated to their post-amputation pain.

PRN medication use will be documented in the diary.

***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. Therapies, such as diathermy (short wave, ultrasound, and microwave) therapy and water therapy, which increase risk to the subject, are not permitted. Other electrical stimulation therapies (e.g., transcutaneous electrical nerve stimulation [TENS]) are not permitted.

**7.4 Eligibility**

Amputees who meet all of the inclusion and exclusion criteria will be eligible to enroll in the study as subjects.

**7.4.1 Inclusion criteria**

- At least 18 years old
- Traumatic lower extremity amputation(s)
- Healed amputation and healthy residual limb based upon the investigator's evaluation
- Post-amputation pain [REDACTED]
- 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)**

[REDACTED] post-amputation pain [REDACTED]

**7.4.3 Exclusion criteria**

- Change of prescribed medications affecting pain [REDACTED] as indicated from subject-reported medication history.
- Beck Depression Inventory (BDI-II) [REDACTED]
- Compromised immune system based on medical history [REDACTED]

- Diabetes Mellitus Types I or II [REDACTED]
- Implanted spinal cord stimulator, cardiac pacemaker/defibrillator or Deep Brain Stimulator
- History of bleeding disorder or subjects who are on antiplatelet or anticoagulation therapies [REDACTED]
- History of valvular heart disease
- Confounding 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 within the last three months 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] sponsored Amputee Pain feasibility trial
- Any other condition that may interfere with ability to participate in a clinical trial [REDACTED] as determined by the Investigator
- Prisoners

**7.4.4 Additional exclusion criteria (verified after initial criteria verification)**

- INR > 1.5 for those on warfarin
- Pregnant [REDACTED]

**7.5 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. [REDACTED]

**7.5.1 Visit 1 - Baseline**

Individuals with one or more lower extremity amputations reporting post-amputation pain [REDACTED] will be considered for enrollment into the study. 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.

The individual's medication affecting pain usage will be reviewed and documented.

[REDACTED]

The individuals who satisfy the preliminary criteria will be asked to complete a [REDACTED] baseline diary to record [REDACTED] for each region of post-amputation pain [REDACTED] the use of medications affecting pain, and the hours of daily prosthetic usage. Individuals must report [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### **[REDACTED] Visit 2 - Lead Placement and Testing [REDACTED]**

Following the baseline visit, individuals who qualify for lead placement [REDACTED] will return to the clinic for placement of the percutaneous leads [REDACTED]

All individuals receiving warfarin therapy will be tested within 2 days prior to the lead placement visit to ensure they meet the inclusion/exclusion criteria with an INR that is not greater than 1.5.

#### **7.5.2.1 Randomization**

Qualifying individuals will be randomized to either Group #1 (Treatment) or Group #2 (Control) using block randomization. [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**7.5.2.6 Home Trial or Subject Disposition**

*At the end of Visit 2, the subject will either:*

- 1) proceed to the home trial,*
- 2) return for another Visit 2, or*
- 3) be terminated from the study*

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

1. Proceed to home trial:

If all leads were placed, the subject will be prepared to proceed to the home trial.



2. Return for another Visit 2:

If there is not sufficient time to complete lead placement or the testing, or if the Group #1 subject does not respond to stimulation, the investigator may present the subject with the option to return for a repeat lead placement visit.

3. Terminate from the study:

If the subject does not wish to continue with further lead placement, they will be terminated from the study if no adverse events (AE) are noted at the 24-48 hour telephone follow-up. If an AE is noted the subject will be followed until the AE resolves.

**7.5.2.7 Bilateral Amputees**

*Bilateral amputees may also receive up to 2 SPRINT Systems for their second leg if it meets the same criteria*



**7.5.2.8 Photography and Video Recording**

The lead placement procedure may be photographed or recorded on video for educational, publication, and training purposes. Subject consent will be obtained for photography or video recording; subject faces or any identifying marks either will be de-identified or will not appear in the pictures and video. Ultrasound imaging collected during lead placement may be obtained and provided to the Sponsor.



**7.5.2.9 Home Trial**

*At the end of Visit 2, subjects will be prepared to proceed to the home trial*

Group #1 subjects will be prepared to proceed to the home trial. The stimulation parameters will be set before the subject leaves the visit. [REDACTED]

Group #2 subjects will be prepared for the home trial. The site will ensure the Stimulator is placed in Sham mode before the subject leaves the visit. [REDACTED]

**7.5.3 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 event (AE). All AEs will be followed until resolution. Subjects who return for Visit 2 but are not eligible to be randomized will not receive a follow-up phone call to assess adverse events following lead placement because they will not have participated in the lead placement procedure.

**7.5.4 Visit 4** [REDACTED]

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

[REDACTED]

[REDACTED]

[REDACTED]

**7.5.5 Visit 5** [REDACTED]

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

[REDACTED]

**Visit 6** [REDACTED]

The subject will return approximately 3 weeks after the initial lead placement [REDACTED]

[REDACTED]

**Visit 7** [REDACTED]

The subject will return approximately 4 weeks after the initial lead placement. This visit is identical to Visit 4, [REDACTED]

[REDACTED]

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

1. Proceed to home trial:

If the subject responds to stimulation [REDACTED]  
the subject will be prepared to proceed to the home trial. [REDACTED]

2. Return for another Visit 2:

[REDACTED]

If there is not sufficient time to complete lead placement or the testing, or if the subject does not respond to stimulation, the investigator may present the subject with the option to return for a repeat lead placement visit.

3. Terminate from the study:

If the subject does not wish to continue with further lead placement, they will be terminated from the study if no adverse events (AE) are noted at the 24-48 hour telephone follow-up. If an AE is noted the subject will be followed until the AE resolves.

**7.5.8 Visit 8 – 5 Weeks Post Lead Placement**

The subject will return approximately 5 weeks after the initial lead placement. [REDACTED]

**7.5.9 Visit 9 – 6 Weeks Post Lead Placement**

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

**7.5.10 Visit 10 – 7 Weeks Post Lead Placement**

The subject will return approximately 7 weeks after the initial lead placement. [REDACTED]

**7.5.11 Visit 11 – EOT**

**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]

**Visit 12 – conducted 1 week after EOT**

Subjects will return to the clinic 1 week after the end of treatment (EOT). [REDACTED]

**7.5.13 Visit 13 – Follow-up visit**

**conducted 1 month (4 weeks) after EOT**

Subjects will return to the clinic 4 weeks after EOT. [REDACTED]

**7.5.14 Visit 14 – Telephone Follow-up  
conducted 2 months (8 weeks) after EOT**

[REDACTED]

**7.5.15 Visit 15 – Telephone Follow-up  
conducted 3 months after EOT**

[REDACTED]

**7.5.16 Visit 16 – Follow-up visit  
conducted 4 months after EOT**

[REDACTED]

**7.5.17 Visit 17 – Telephone Follow-up  
conducted 5 months after EOT**

[REDACTED]

**7.5.18 Visit 18 – Telephone Follow-up  
conducted 6 months after EOT**

[REDACTED]

[REDACTED]

[REDACTED]

**7.5.19 Visit 19 – Telephone Follow-up  
conducted 7 months after EOT**

[REDACTED]

**7.5.20 Visit 20 – Telephone Follow-up  
conducted 8 months after EOT**

[REDACTED]

**7.5.21 Visit 21 – Telephone Follow-up  
conducted 9 months after EOT**

[REDACTED]

**7.5.22 Visit 22 – Follow-up visit  
conducted 10 months after EOT**

### 7.5.23 Unscheduled visits/Lead Replacements

Subjects may need to return to the clinic for an unscheduled visit if they experience an adverse event that requires further evaluation [REDACTED] experience a technical issue with the system, or require a bandage change or lead replacement. [REDACTED]

### 7.5.24 Study Visit Windows

The acceptable windows for each visit are listed in Table 3.

**Table 3 Study Visit Windows**

| Visit Number | Visit Name          | Window     |
|--------------|---------------------|------------|
| n/a          | Consent             | [REDACTED] |
| 1            | Baseline            | [REDACTED] |
| 2            | Lead Placement      | [REDACTED] |
| 3            | Telephone Follow-up | [REDACTED] |
| 4            | 1 week Stimulation  | [REDACTED] |
| 5            | 2 week Stimulation  | [REDACTED] |
| 6            | 3 week Stimulation  | [REDACTED] |
| 7            | 4 week Stimulation  | [REDACTED] |
| 8            | 5 week Stimulation  | [REDACTED] |
| 9            | 6 week Stimulation  | [REDACTED] |

|    |                          |  |  |
|----|--------------------------|--|--|
| 10 | 7 week Stimulation       |  |  |
| 11 | 8 week Stimulation / EOT |  |  |
| 12 | 1 week post EOT          |  |  |
| 13 | 1 month post EOT         |  |  |
| 14 | 2 months post EOT call   |  |  |
| 15 | 3 months post EOT call   |  |  |
| 16 | 4 months post EOT        |  |  |
| 17 | 5 months post EOT call   |  |  |
| 18 | 6 months post EOT call   |  |  |
| 19 | 7 months post EOT call   |  |  |
| 20 | 8 months post EOT call   |  |  |
| 21 | 9 months post EOT call   |  |  |
| 22 | 10 months post EOT       |  |  |

### 7.6 Early termination

[REDACTED]

### 7.7 Subject compensation

Individuals [REDACTED]

[REDACTED] will receive [REDACTED] compensation for full participation in all study visits to cover expenses while taking part in this study. Compensation will be disbursed as individuals complete certain milestones within the study. [REDACTED]

The disbursement schedule will be as follows:

- [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 4-13, Visit 16, and Visit 22
- [REDACTED] after the completion of each Visit 14, 15, and 17-21 phone calls

If a subject volunteers to participate in an additional study visit #2 (returns for another session of stimulation testing) the subject will receive [REDACTED] compensation at the completion of that visit. If a Group #2 subject requires lead replacement after Visit 4, the subject will receive [REDACTED] compensation at the completion of the replacement.

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]

[REDACTED]



## 8.0 Data management

### 8.1 Subject screening and identification logs

A subject screening log will be completed at each investigational site for all subjects who were considered for the study. 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.

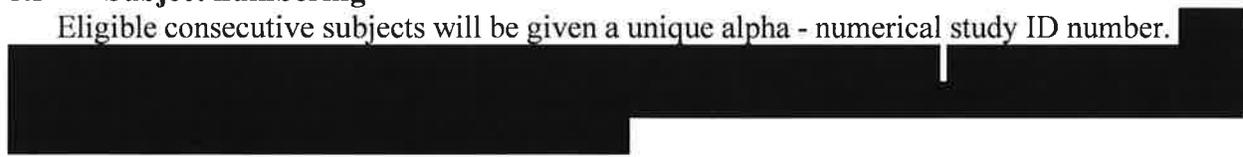
Paper source documents, where applicable, will be completed and maintained in a fashion that is consistent with accepted Good Clinical Practices. If necessary, corrections to the source documentation will be made by using a single line strikeout with the initials and date of the person making the correction. 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, all 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.

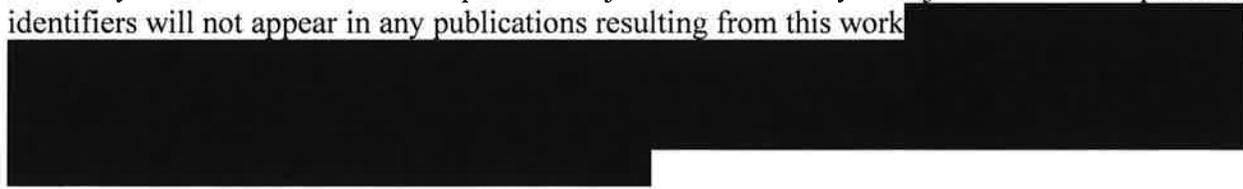
### 8.3 Subject numbering

Eligible consecutive subjects will be given a unique alpha - numerical study ID number.



### 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]

[REDACTED]

**9.0 Outcome analysis**

All primary and secondary endpoint data will be analyzed and reported. This study is a randomized placebo-controlled [REDACTED] study. The goal of the study is to gather data regarding the safety and effectiveness of percutaneous PNS for the treatment of post-amputation pain. Descriptive statistics will be used to summarize baseline subject characteristics within each treatment group. Baseline characteristics include both demographic variables as well as variables such as baseline pain intensity, time elapsed from amputation, medications affecting pain used at baseline, prosthesis fit, and the baseline BDI-II score. These characteristics will be examined via a covariate analysis.

[REDACTED]

**9.1 Primary clinical efficacy endpoint analysis**

[REDACTED]

The effectiveness of percutaneous Peripheral Nerve Stimulation (PNS) for the treatment of post-amputation pain will be assessed in the present study. The goal of the proposed [REDACTED] study is to determine if the investigational treatment produces pain relief that is clinically meaningful and greater than the placebo effect. To distinguish between the effect of the investigational treatment and the placebo effect, qualifying individuals will be randomized (1:1) to either Group #1 (Treatment) or Group #2 (Control). The groups will be identical except for whether active stimulation (Group #1) or sham stimulation (Group #2) is delivered during the first 4 weeks of the home trial. Both groups are expected to experience a similar placebo effect from the study procedures and use of the devices. In Group #1, subjects will experience both the placebo effect and the investigational treatment effect. During the sham stimulation phase in Group #2, subjects will experience only the placebo effect. Thus, if there is a difference between the mean improvements during sham stimulation and active stimulation, it can be attributed to the investigational treatment effects.

The null hypothesis ( $H_0$ ) is that the investigational treatment (Group #1, active simulation) is equal to the control (Group #2, sham stimulation) in providing pain relief. The alternative hypothesis ( $H_1$ ) is that Group #1 has a proportion of successes that is not equal to the proportion of successes of Group #2.

1.  $H_0$ : proportion of successes of Group #1 = proportion of successes of Group #2
2.  $H_1$ : proportion of successes of Group #1  $\neq$  proportion of successes of Group #2

If the proportion of successes of the investigational treatment is statistically significantly greater ( $p < 0.05$ ) than the proportion of successes of the control during the first 4 weeks of the home trial and the alternative hypothesis is accepted at the 0.05 level of significance, it will indicate that the investigational treatment is clinically significant and different than the placebo effect<sup>95</sup>.

Pain relief will be evaluated using the average pain intensity. All regions of post-amputation pain (RLP or PLP or both) that have intensities  $\geq 4$  on average during the baseline period and receive treatment with an investigational device will be used to assess the primary efficacy endpoint. All amputees will record two daily post-amputation pain scores (one daily score for RLP and one daily score for PLP) for each amputated leg in the 7-day diaries using BPI-SF Question #5. For each individual, the region(s) of post-amputation pain with a 7-day average  $\geq 4$  during baseline in a leg that receives blinded treatment from an investigational device(s) will qualify to be used in the determination of clinically-meaningful success for that subject throughout the study. Each amputee must have  $\geq 50\%$  reduction in all areas of qualifying RLP and PLP to be considered a success in the primary effectiveness endpoint analysis.

The primary endpoint of the study compares the proportion of subjects in Group #1 relative to that in Group #2 that achieve  $\geq 50\%$  reduction in all areas of qualifying post-amputation pain from baseline to the first 4 weeks of the home trial, examining the statistical superiority of proportion of clinical successes of Group #1 over the proportion of successes of Group #2. The post-amputation pain intensity 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 the first 4 weeks of the home trial (*i.e.*, the average of all diary scores during this period). For each leg with leads, the average pain scores will only include the days when all leads are in place (e.g., if leads are placed in second leg during week 2 of home trial, then only the data from weeks 2-4 will be used). Data will be collected as described in the Schedule of Procedures (Appendix A).

**9.1.1 Baseline characteristics and changes in usage of medication affecting pain will be analyzed to determine how strong their relationships are with changes in pain intensity between baseline and EOT**

The following variables: sex, age, baseline pain intensity, time elapsed from amputation, medications affecting pain used at baseline, prosthesis fit, baseline BDI-II score, and percent changes in usage of medication affecting pain between baseline and EOT (i.e., PRN medication usage) will be examined via a covariate analysis to determine their influence on the primary outcome.

**9.1.2 A power analysis of the 2-tailed, 2-sample Mann-Whitney test was conducted for the primary efficacy endpoint to determine the sample size for > 90% power and a 5% significance level**

A power analysis of the 2-tailed, 2-sample Mann-Whitney test was conducted with data from the previous feasibility study and data published in other studies. The proportion of successes expected for Group #1 was estimated from the previous feasibility study in which stimulation produced comfortable sensations (paresthesia) in the region of greatest pain. The proportion of successes expected for Group #2 was estimated from published studies in which sham (placebo) treatments were given to amputees with post-amputation pain. The null hypothesis that the proportion of successes of Group #1 is equal to the proportion of successes of Group #2 was tested.

[REDACTED]

[REDACTED]

**9.1.4 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]

[REDACTED]

[REDACTED]

[REDACTED]

### 9.1.5 Imputation of missing diary data during the home trial will be performed conservatively

Data missing from any day of diary during the first 4 weeks of the home trial will be imputed from baseline diary data, using the average pain score from the baseline week. Scores will only be imputed if recall data are unavailable and cannot be obtained.

[REDACTED]

### 9.2 Safety endpoint analysis

All adverse events will be documented, reported, and categorized so that we may further understand the safety profile of this approach. Knowledge gained from this study will further refine consent forms and the risk benefit profile for future studies.

### 9.3 Secondary clinical efficacy endpoint analysis

Additional endpoints below will be assessed to document further the effectiveness of using the SPRINT Peripheral Nerve Stimulation (PNS) System for the symptomatic relief and management of post-amputation pain.

- Durability of the treatment effect on average pain intensity (Primary Endpoint) after 8-week home trial

The durability of the treatment effect on average pain intensity compares the proportion of subjects who successfully achieve  $\geq 50\%$  reduction from baseline in Group #1 at end of 8-week home trial relative to that in Group #2 at end of 4-week sham period, examining the statistical superiority of the proportion of successes of Group #1 over the proportion of successes of Group #2. The post-amputation pain intensity scores will be determined for each subject by applying the same method used for the primary endpoint: 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 the 8 weeks of treatment (*i.e.*, the average of all scores in the diaries during this period) for Group #1. To be

considered a success, subjects must have  $\geq 50\%$  reduction in all qualifying regions of pain, defined as regions of RLP and PLP with a baseline pain score  $\geq 4$  that received blinded treatment. The proportion of successes in Group #1 will be compared to the proportion of successes in Group #2 during the sham stimulation phase (Weeks 1-4 of the home trial). The null hypothesis is that there is no difference in success rates between the two treatment groups, versus the alternative hypothesis, that the success rates differ from one another.

- Durability of the treatment effect on average pain intensity (Primary Endpoint) at monthly intervals after start of therapy (3 - 12 months after start)

The analysis of the durability of the treatment effect on average pain intensity compares the proportion of subjects who successfully achieve  $\geq 30\%$  reduction from baseline in Group #1 relative to that in Group #2, examining the statistical superiority of the proportion of successes of Group #1 over the proportion of successes of Group #2. The average post-amputation pain intensity scores will be determined for each subject using BPI-SF Question #5 with 1 week recall. For Group #1, the scores reported at Visit 2 (prior to lead placement) will be compared to the score for the same region(s) of pain at each monthly interval after the end of the 8-week home trial (i.e., during the monthly follow-up calls/visits from months 3-12 after start of therapy). For Group #2, the scores reported at Visit 2 (prior to lead placement) will be compared to the score for the same region(s) of pain during the final week of the 4-week sham period. To be considered a success, subjects must have clinically-significant reduction ( $\geq 30\%$ ) from baseline in all qualifying regions of pain, defined as regions of RLP and PLP with a baseline pain score  $\geq 4$  that received blinded treatment. The proportion of successes in Group #1 at each monthly visit will be compared to the proportion of successes in Group #2 at the end of the sham period. For each month, the null hypothesis is that there is no difference in success rates between the two treatment groups, versus the alternative hypothesis, that the success rates differ from one another. Testing will be conducted at the 0.05 level of significance.

- Pain interference (BPI-SF Question #9) at monthly intervals after start of therapy

The analysis of the treatment effect on pain interference compares the proportion of subjects who successfully achieve  $\geq 50\%$  reduction in average pain interference score in Group #1 relative to that in Group #2, examining the statistical superiority of the proportion of successes of Group #1 to that of Group #2. In Group #1, the baseline average pain interference score (BPI-SF Question #9) will be compared to the average pain interference score for the same region(s) at each monthly interval after start of therapy. In Group #2, the baseline average pain interference score will be compared to the score at the end of the 4-week sham period. To be considered a success, subjects must have  $\geq 50\%$  reduction in the average pain interference score of all qualifying regions of pain, defined as regions of RLP and PLP with an average baseline pain interference score  $\geq 4$  that received blinded treatment. The null hypothesis is that there is no difference in success rates between the two treatment groups (i.e., Group #1 at the monthly interval vs. Group #2 at end of sham period), versus the alternative hypothesis, that the success rates differ from one another. Testing will be conducted at the 0.05 level of significance.

- Pain disability (Pain Disability Index (PDI)) at monthly intervals after start of therapy

The analysis of treatment effect on pain disability compares the proportion of subjects who successfully achieve  $\geq 10$  point reduction in PDI scores from baseline in Group #1 relative to that of Group #2, examining the statistical superiority of the proportion of successes of Group #1 to that of Group #2. <sup>96</sup>The baseline PDI score will be compared to the PDI score at end of first 4 weeks, at the end of the home trial, and at monthly intervals after end of therapy (3-12 months after start of therapy). In Group #1, the baseline PDI score will be compared to the PDI score at each monthly interval after start of therapy. In Group #2, the baseline PDI score will be compared to the score at the end of the 4-week sham period. To be considered a success, subjects must have a  $\geq 10$  point reduction in PDI. The null hypothesis is that there is no difference in success rates between the two treatment groups (*i.e.*, Group #1 at the monthly interval vs. Group #2 at end of sham period), versus the alternative hypothesis, that the success rates differ from one another. Testing will be conducted at the 0.05 level of significance.

- Depression (Beck Depression Inventory (BDI-II)) at monthly intervals after start of therapy

The analysis of treatment effect on depression examines the statistical superiority of the mean percent improvement from baseline at monthly intervals of Group #1 relative to that of Group #2. In Group #1, the baseline BDI-II score (assessed at Visit 1) will be compared to the BDI-II score at each monthly interval after start of therapy. In Group #2, the baseline BDI-II score will be compared to the score at the end of the 4-week sham period. The null hypothesis is that there is no difference in mean percent improvement between the two treatment groups (*i.e.*, Group #1 at the monthly interval vs. Group #2 at end of sham period), versus the alternative hypothesis, that the mean percent improvements differ from one another. Testing will be conducted at the 0.05 level of significance.

- Analgesic usage

The analysis of treatment effect on analgesic usage will evaluate the change in opioid analgesic usage separately from the change in non-opioid analgesic usage (see Exploratory Measures, Section 9.4).

Changes in opioid analgesic usage will be calculated using morphine equivalent dosing (MED) to compare the mean percent change from baseline to the end of first 4 weeks in Group #1 relative to that of Group #2. Analysis will be conducted to determine if the mean change of Group #1 is statistically significantly greater than the mean improvement of the Group #2<sup>103-106</sup>. The change in the opioid analgesic usage will be determined for subjects (who are receiving prescribed opioid medications at baseline) by taking the mean of the daily MED for the entries reported in the 7-day diary at baseline compared to the mean of the daily MED for the entries reported in the 7-day diary during the week before Visit 7 (*i.e.*, week 4 of home trial). The null hypothesis is that the mean change in MED is not significantly different in both groups, and the alternative hypothesis is that the mean change for the two groups differ.

The change in MED at the end of the 8-week home trial will also be calculated. For Group #1, the change in the opioid analgesic usage will be determined for subjects (who are receiving prescribed opioid medications at baseline) by taking the mean of the daily MED for the entries reported in the 7-day diary at baseline compared to the mean of the daily MED for the entries reported in the 7-day diary during the week before Visit 11 (*i.e.*, week 8 of home trial). This will be compared to the mean change in MED during week 4 of the home trial in Group #2 (*i.e.*, final week of the sham period), as calculated in the

previous analysis. The null hypothesis is that the mean change in MED is not significantly different in both groups, and the alternative hypothesis is that the mean change for the two groups differ.

- Prosthetic usage (hours of daily prosthetic usage recorded in diary) at end of first 4 weeks and after 8-week home trial
- The analysis of treatment effect on the prosthetic usage compares the mean rank scores (of 25 possible ranks, ranging from 0 to 24 hours) at baseline to the end of first 4 weeks and after the 8-week home trial of Group #1 relative to that of Group #2, examining the statistical superiority of the mean rank scores of Group #1 over that of Group #2. The mean rank scores will be determined for each subject by taking the 7-day mean of the daily hours of prosthetic usage reported in the 7-day diary at baseline (for the residual limb with the region of pain being used for primary efficacy) compared to the 7-day mean of the daily hours of prosthetic usage reported in the diary during the week before Visit 7 and the last week of stimulation before the end of the 8-week home trial. The null hypothesis is that the mean rank scores for both groups are not significantly different. The alternative hypothesis is that the mean ranks scores for the two groups differ.
- Subject Satisfaction Survey  
A survey will be administered to the subjects at EOT to assess their satisfaction with the study and device.

#### 9.4 Exploratory endpoint analysis

Exploratory endpoints will be analyzed to provide information on additional outcome measures and how the system and subject characteristics affect the outcome of the investigative treatment on post-amputation pain. For all endpoints, data will be collected as described in the Schedule of Procedures (Appendix A).

- Treatment effect in Group #2  
Group #2 will receive stimulation during the second half of the home trial (Weeks 5-8), and the proportion of successes and/or mean improvements in outcome measures during this phase will be compared to those during the sham stimulation phase. In addition, a repeated measures analysis may be conducted to determine the within-subjects improvement from sham to stimulation.

Global impression of change (Patient Global Impression of Change (PGIC))

Analyses of changes in average RLP

[REDACTED]

Analyses of changes in average PLP [REDACTED]

Analyses of changes in worst RLP [REDACTED]

Analyses of changes in worst PLP [REDACTED]

[REDACTED]

- Non-opioid medication usage

[REDACTED]

- Pain Catastrophizing Scale (PCS)

[REDACTED]

- Clinician Satisfaction Survey

[REDACTED]

### 9.5 Per Protocol and Intent to Treat Analyses

Analyses of the primary and secondary effectiveness endpoints will be conducted on the intent-to-treat (ITT) population and the per-protocol (PP) population at each specified study interval defined as follows:

PP Population: The per-protocol population will consist of all randomized subjects who meet the following criteria:

- Were implanted [REDACTED]
- For Group #1 subjects: paresthesia coverage in the target areas.
- Have an adequate number of average pain intensity (BPI-5) scores in the diaries during the primary endpoint period (*i.e.*, first 4 weeks of home trial). These diaries must not be missing more than 50% of the pain scores to be included in the PP population.

[REDACTED]

- Continued study eligibility (subjects cannot have a change in medical status that would have otherwise excluded them from the study)

ITT Population: The intent-to-treat population will include all randomized patients who were implanted [REDACTED] that is, patients will be analyzed according to the treatment group to which they were randomized. Evaluable subjects are defined as those who were randomized and implanted with a lead.

## 10.0 Study monitoring

### 10.1 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 Investigational Site team.

### 10.2 Routine monitoring

Monitoring visits to the Investigational 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 Investigational Plan 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. In addition, source documents will be reviewed for accuracy against data found on the Case Report Forms.

[REDACTED]

### 10.3 Device accountability

Device accountability will be maintained by the Investigational Site.

[REDACTED]

#### 10.3.1 Returning used devices to SPR Therapeutics

The sites will record any devices returned to SPR Therapeutics in the Device Accountability Log. They will obtain a Return Goods Authorization (RGA) number by calling SPR Therapeutics.

[REDACTED]

[REDACTED]

[REDACTED]

**10.3.2 Disposal of system components**

Disposal of all System components must comply with national and local laws governing the disposal of biohazardous waste. [REDACTED]

**10.4 Designation of study monitor**

The monitor for this study will be:

[REDACTED]

SPR Therapeutics, Inc.  
22901 Millcreek Blvd., Suite 110  
Cleveland, OH 44122

[REDACTED]

Other appropriately qualified clinical monitors may also be involved in the monitoring of study sites.

#### **10.5 Independent research monitor (i.e., independent medical monitor or safety officer)**

The independent research monitor will be [REDACTED] has extensive experience conducting clinical research and is educated in the area of study subject rights. In addition, he is trained in the protection of human subjects.



All safety and effectiveness data will be supplied to and reviewed by the independent research monitor in a blinded fashion, so that the centers/investigators cannot be identified. If after a review of the data, the independent research monitor feels the necessity to review any un-blinded data, such a request will be made to the Sponsor and the final decision will be made by the Sponsor. The data supplied to the independent research monitor will not include any Protected Health Information regarding the study participants.

#### **11.0 Adverse events and adverse device effects**

Adverse events (AEs) that occur during the study will be captured on case report forms (CRFs). Specific details regarding any observed AE will be collected on a separate Adverse Event Form. The severity of each Adverse Event will be collected as well as its relationship to the System. AEs will be classified as mild (event that causes mild discomfort or inconvenience and resolves without treatment), moderate (event that requires medical intervention or medication to treat), or severe (event that requires intervention to prevent permanent impairment or damage, an event that requires or prolongs hospitalization, or an event that is disabling, causing permanent damage, life threatening, or causing death). Any necessary treatment or intervention required and the resolution status of the adverse event will also be documented. Adverse Events will be followed to resolution.

An Adverse Device Effect (ADE) is a device-related Adverse Event. 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 Investigational Plan or application or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.



Table 5 Unanticipated Adverse Device Event Sponsor Contact Information

| UNANTICIPATED ADVERSE DEVICE EVENT<br>SPONSOR CONTACT INFORMATION |               |                  |            |
|---|---------------|------------------|------------|
| Name/Title  | Email address | Telephone Number | Fax Number |
| [REDACTED]  | [REDACTED]    | [REDACTED]       | [REDACTED] |
| [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 device related, will be reported as well. SPR Therapeutics is responsible for furnishing the required information to the appropriate regulatory authorities.

**12.0 Risk benefit analysis**

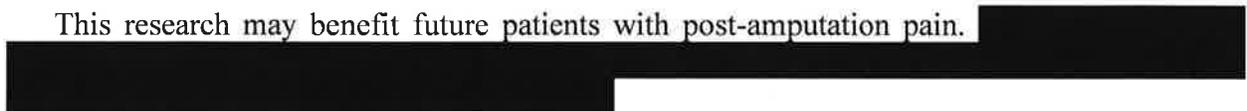
The potential risks and benefits to study subjects participating in this study are listed below.

**12.1 Potential benefits**

Subjects in this study may not receive any direct benefit by participating in this study. If the treatment is successful, subjects may experience some or all of the following benefits during and/or after stimulation:

- A possible reduction in the intensity of pain
- A possible reduction in degree to which pain interferes with the ability to perform daily tasks (pain interference).

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





[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**■ Risk of skin irritation under the SPRINT Pad, Smartpatch Lead Connector Tape, bandages, or belt**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**Risk of discomfort or increased pain**

[REDACTED]

**12.3 Risk analysis**

As described above, all efforts will be made to mitigate each potential risk associated with the use of the system. Despite all attempts to mitigate the risks associated with the use of the system, it is possible that these events and other unanticipated events may occur. If the treatment is successful, subjects may have a reduction in pain during the treatment period. In addition, it is possible that some patients may experience a longer treatment effect beyond the stimulation period. Though the possibility exists that patients may experience no benefit to participating in this study, the knowledge gained from the results and the application of that knowledge toward the development of a system to relieve post-amputation pain may benefit future patients and significantly improve the quality of life for other patients suffering from post-amputation pain. The potential risks of participation in this study have been minimized such that they are unlikely to occur. The knowledge gained from the study and the potential for temporary relief of pain justifies the minimal potential risk.

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

[REDACTED]

[REDACTED]

[REDACTED]

- 13.0 Ethical considerations
- 13.1 Declaration of Helsinki

[REDACTED]

The study will be performed in accordance with the relevant parts of the ICH Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki, and the FDA regulations.

### **13.2 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.

In addition, a list of the IRB members and their titles will be obtained by the Investigator and maintained in the study regulatory files. Copies of both the IRB member list and the protocol and consent approvals will be furnished to SPR Therapeutics prior to any shipment of Investigational Devices.

### **13.3 Informed consent form**

In accordance with 21 CFR 812, 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. 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. Modifications to the Consent Form must be approved by SPR Therapeutics prior to submission to the IRB. The investigator must also inform SPR Therapeutics of any IRB mandated revisions to the study protocol.

### **13.4 Amending the protocol**

This study will be carried out in accordance with this Study Protocol/Investigational Plan. 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.

## **14.0 Study administration**

### **14.1 Record retention**

By signing this study protocol, 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. The Investigator will be required to retain all records required by this study during the

investigation and for a period of 2 years after the later of the following two dates: The date of which the investigation is terminated or completed or, the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol. The investigator must inform SPR Therapeutics if the location of the records changes or if there are any plans to destroy the records.

[REDACTED]

#### **14.3 Criteria for terminating a center**

SPR Therapeutics 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]

#### **14.4 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 investigational device.

[REDACTED]

[REDACTED]

[Redacted]

SPR Therapeutics, LLC.

[Redacted]

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[REDACTED]

[REDACTED]

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SPR Therapeutics, LLC.

[REDACTED]

