SPR Therapeutics

TO: FILE (Protocol 0141-CSP-000, NCT 02468934)

FROM: SPR Therapeutics, INC

DATE: July 17, 2018

RE: Conversion from LLC to Corporation and Registration of SPR

The attached protocol (0141-CSP-000) for the NCT study number 02468934 was last revised in November 2015. Since that time, SPR Therapeutics converted from an LLC to a Corporation. The conversion of SPR Therapeutics, LLC to SPR Therapeutics, INC was completed on September 8, 2017. As a result, the attached protocol reflects the company status (SPR Therapeutics, LLC) at the time of execution of this protocol.

In addition, since the time of this protocol, the SPRINT® trademark for the device mentioned in the protocol has registered with the USPTO.

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A Prospective Case Series Study of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement

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Protocol 0141-CSP-000

Amendment Date(s): July 16, 2015
November 13, 2015

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.

TABLE OF CONTENTS

Protocol Synopsis

Title	A Prospective Case Series Study of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement
Investigational (Test) Device	The percutaneous fine-wire Smartpatch MicroLead™ that delivers electrical stimulation via connection to the SPRINT™ Peripheral Nerve Stimulation (PNS) System, an investigational external battery-powered stimulator and accessory components. Up to two leads and stimulators will be used in each subject (*i.e.*, 1 lead per stimulator).
Study Design	Prospective Case Series Feasibility Study
Primary Study Objective	To determine the treatment effect of PNS therapy for the treatment of knee pain following TKA
Study Plan	Individuals undergoing a primary unilateral TKA will be considered for enrollment into the study. After obtaining informed consent, potential subjects will be evaluated for general eligibility. Up to 2 weeks prior to TKA surgery, up to two leads will be placed percutaneously [redacted]. Stimulation will be applied to determine optimal stimulus parameters and lead locations. Stimulation may be delivered up to the time of the TKA. Prior to the TKA surgery, the leads will be disconnected from the stimulators and remain indwelling (secured beneath waterproof bandages) until after the completion of the TKA surgery. Following the TKA surgery [redacted], leads will be connected to Sprint stimulators. Stimulation will be turned on and stimulation parameters adjusted as needed [redacted]. Subjects will receive treatment for up to 24 hours/day for up to 8 weeks [redacted]). At the conclusion of the treatment period, the leads will be removed, and subjects will be followed until 3 months after the TKA surgery. Subjects will be permitted to use analgesic medications, and analgesic usage will be recorded. For surgical anesthesia, subjects will not be allowed to receive any blocks in the upper thigh/buttocks [redacted] or blocks in any location using long lasting agents [redacted] Postoperatively, subjects will not be allowed to receive continuous regional nerve blocks. Subjects will complete a daily diary recording their medication usage and "Average Pain" (Brief Pain Inventory, question 5) for each day of the treatment period. Other outcomes that will be assessed include tests of function, stimulation characteristics, surveys/questionnaires, and collection of pain scores and pain treatments. Outcomes will be assessed based on the schedule of procedures (Appendix A).
Sites (N)	Up to 6 investigational sites
Subjects (N)	Up to 36 subjects

Inclusion Criteria	• At least 21 years old • Scheduled to undergo a primary unilateral total knee replacement procedure • Able to understand and willing to take part in study and comply with all study requirements
Exclusion Criteria	• Body Mass Index (BMI) > 40 kg/m^2 • [redacted] Compromised immune system based on medical history [redacted] • History of valvular heart disease • Implanted cardiac pacemaker/defibrillator or Deep Brain Stimulator • Evidence of joint or overlying skin infection of the affected limb • History of recurrent skin infections • Bleeding disorder **OR** INR ≥ 1.5 for those on warfarin • [redacted] Confounding conditions [redacted] • [redacted] History of nerve damage in the affected lower limb [redacted] • Allergy to skin surface electrodes and/or medical-grade adhesive tapes • Allergy to all local anesthetic agents such as lidocaine or previous reaction to anesthesia • Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator • Prisoners, minors, legally incompetent people, unconscious patients, house staff, or students • Pregnant • History of substance abuse within 6 months • Potential secondary gain issues [redacted]
Primary Safety Endpoint	Occurrence of device-related adverse events.
Primary Clinical Endpoint	Subjects will record average pain while walking over the last 24 hours in a daily diary using the 11-point numerical rating scale (0=no pain to 10=worst pain imaginable) of the Brief Pain Inventory – Short Form (Question 5; BPI-5). The mean of the daily scores recorded [redacted] will be calculated, and the primary endpoint is the mean pain score across all subjects. The primary endpoint will be compared to historical controls (e.g., published data).
Secondary Endpoints	Pain-related outcomes • Pain intensity over the last 24 hours as recorded as **Average pain** on a numerical rating scale (BPI-5) using a daily diary • Pain intensity over the last 24 hours as recorded as **Average pain at rest** on a numerical rating scale (BPI-5) using a daily diary • **Cumulative analgesic usage**

	• **Opioid-related side effects** (*e.g.,* nausea and vomiting, constipation, urinary retention, pruritis, drowsiness, respiratory depression)
	Functional outcomes
	[redacted]**Range of motion (ROM)** ([redacted]
	  ○ Number of days to achieve key milestones in affected knee (*e.g.,* 90 degree flexion)
	  ○ Pain scores before, during, and after ROM testing
	• **Timed Up and Go (TUG)** test
	• **6 minute walk test (6MWT)**
	• **Fixed distance walk test**
	Surveys
	• Change in pain, physical function, and stiffness as measured by the **Western Ontario McMaster University Osteoarthritis Index (WOMAC)**
	• **Pain interference** with activities of daily living as recorded on numerical rating scale (BPI-9)
	• **Patient Global Impression of Change (PGIC)**
	• **Pain Catastrophizing Scale (PCS)**
	• **Time to meet recovery milestones** (e.g., discharge date)
	• Subject satisfaction with the study and therapy as measured by a **Subject Satisfaction Survey**

Exploratory Measurements	• Analyses of primary and secondary endpoints at study intervals not specified in Section 3.0 • Subject-shaded **diagrams of pain and paresthesia** • **Clinician Satisfaction Survey**
Key Demographic Information	• Body Mass Index (BMI) [redacted]Surgical approach [redacted] • Use of post-operative drains • Type of knee implant used (*i.e.,* manufacturer and model)

1.0 GENERAL INFORMATION

1.1 Title of Investigation

A Prospective Case Series Study of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement

1.2 Sponsor Name and Address

SPR Therapeutics
22901 Millcreek Boulevard, Suite 110
Cleveland, OH 44122
Phone: 216-378-9108
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1.3 Materials

The SPRINT™ Peripheral Nerve Stimulation (PNS) System

Up to two Sprint Systems will be used by each subject (i.e., 1 lead per stimulator).

1.4 Indications for Use

The Sprint System is indicated for use for the symptomatic relief and management of knee pain following total knee arthroplasty.

1.5 Study Objective

To determine the treatment effect and safety of PNS therapy for the treatment of knee pain following TKA.

2.0 INTRODUCTION AND BACKGROUND

2.1 Introduction

The goal of this research is to gather data regarding the safety and effectiveness of the SPRINT™ PNS System for the treatment of pain following total knee arthroplasty (TKA; a.k.a. total knee replacement). In 2010, approximately 719,000 TKA procedures were performed in the U.S. to treat disabling knee conditions (*e.g.,* osteoarthritis), and this number is expected to grow to 3.5 million procedures per year by 2030 (Center for Disease Control, 2010, Kurtz et al. 2007). However, a large proportion of TKA patients continue to have poor function for months after surgery. This leads to reduced quality of life (QoL), productivity, and independence. One of the primary causes is postoperative pain, which inhibits early rehabilitation and can lead to chronic pain (Capdevila et al. 1999, Peters et al. 2007, Puolakka et al. 2010, Sinatra 2010). Approximately half (30-90%) (Anderson et al. 2009, Dahlen et al. 2006, Strassels et al. 2004, Choy et al. 2011, Brander et al 2003) of all patients experience moderate to severe pain during the first 2 months after TKA surgery, and prolonged postoperative pain decreases QoL (Chelly et al. 2001, Forrest et al. 1999, Ilfeld et al. 2007, Liu et al. 2012, Mahoney et al. 1990, Panel 1997, Sinatra 2010, Strassels et al. 2004, Wang et al. 2002).

Postoperative pain greatly reduces patient comfort and increases the use of opioids and the length of hospital stay, which increases medical costs (Panel 1997; Rosenquist and Lederhaas 1999; Chelly et al. 2001; Wang et al. 2002). Also, postoperative pain limits knee range of motion and patient tolerance of rehabilitation exercises, which delays return to normal functioning (Shoji et al. 1990; Ryu et al. 1993; Dahlen et al. 2006; Reuben et al. 2008). In addition, uncontrolled acute pain can lead to chronic pain.

Existing treatments for postoperative pain include analgesics, continuous passive motion, cooling pads, epidural analgesia, and regional nerve blocks (anesthetic delivered continuously through a percutaneously placed catheter or as single injections). In spite of these treatments, most patients experience moderate to severe acute pain. Further, during the subacute phase, these treatments are ineffective, are not indicated for such an extended period of time or for at home use, and/or carry risks of side effects and complications. As a result, a non-opioid treatment is needed that can relieve postoperative pain following TKA with minimal side effects and can be used throughout the duration of the subacute phase. The proposed study will determine the feasibility of using PNS therapy to treat postoperative pain following TKA. The hypothesis is that percutaneous stimulation will evoke a [redacted] sensation [redacted] in the region of pain and produce clinically significant reductions in pain.

Subjects will receive leads to stimulate the nerves innervating the regions of pain or expected pain [redacted]) up to 2 weeks prior to TKA surgery. Stimulation may be delivered up to the time of the TKA. Following TKA, stimulation will be turned on and adjusted as needed to provide pain relief. Subjects will record average pain over the last 24 hours in a daily diary using the 11-point numerical rating scale (0=no pain to 10=worst pain imaginable) of the Brief Pain Inventory – Short Form (Question 5; BPI-5). The mean of the daily scores recorded from POD0 to POD28 (i.e., first 4 weeks following TKA surgery) will be calculated, and the primary endpoint is the mean pain score across all subjects, which will be compared to historical controls (e.g., published data). Subjects will receive treatment for up to 24 hours/day for up to 60 days (*i.e.,* leads will be indwelling for up to 60 days total). Subjects will be followed for three months following TKA surgery. The results of this study will [redacted] will be used to support subsequent studies of the SPR PNS therapy to treat postoperative pain following TKA.

2.2 Background

Postoperative pain following total knee arthroplasty is a substantial medical problem
Total knee arthroplasty (TKA, i.e., total knee replacement) is a surgical treatment for painful and debilitating knee conditions, such as osteoarthritis (OA), which affects 5% of adults (9-18 million people) (Murphy & Helmick 2012, Neogi & Zhang 2013, London et al. 2011). In the U.S., approximately 719,000 TKA procedures were performed in 2010 (CDC, 2010), and this number is expected to grow to 3.5 million procedures per year by 2030 (Kurtz et al. 2007).

The first 4 weeks following TKA surgery are a critical period for physical rehabilitation, which is essential for functional recovery following TKA. Adequate levels of quadriceps strength and knee range of motion are required for activities of daily living (Jones et al. 2003). However, during the first 4 weeks, quadriceps strength is diminished substantially by 48-60% (Bade et al. 2010, Bade & Stevens 2011, Mizner et al. 2005), and knee range of motion is diminished (Su et al. 2010).

Patients that can undergo early and intense rehabilitation can minimize the loss of quadriceps strength and prevent knee stiffness (*i.e.,* reduced range of motion), resulting in greater long-term functional outcomes exceeding preoperative levels (Shoji et al 1990, Bade & Stevens 2011). However, the start of physical rehabilitation and the intensity and duration of rehabilitation are limited by both existing pain and the fear of inducing additional pain (Ryu et al. 1993, Bade & Stevens 2011). This delay and reduced intensity of therapy often impedes recovery, and up to 27% of patients (up to 194,000 new cases/year) have not achieved full functional recovery ≥1 year following surgery (Jones et al. 2003, Singh et al. 2010).

Approximately half (30-90%) (Andersen et al. 2009, Dahlen et al. 2006, Strassels et al. 2004, Choy et al. 2011, Brander et al 2003) of all TKA patients experience moderate to severe pain during the first month after TKA surgery that can interfere with rehabilitation during this critical period, resulting in impaired function for several months following TKA. Over half of TKA patients (52%) are unable to walk 30 minutes without severe pain at 6 months after TKA, and 17% have severe pain while walking any distance at 1 year after TKA (Dawson et al. 1998). Also, walking speed at 1 year after TKA is 18% slower overall and 51% slower on stairs compared to individuals with healthy knees (Walsh et al. 1998), and 60-80% of TKA patients experience difficulty climbing stairs several months to years after TKA (Jones et al. 2003, Bade & Stevens 2011, Walsh et al. 1998). In addition, 64-84% of patients have difficulty with other activities of daily living ≥6-12 months following TKA, (*e.g.,* work, getting in/out of a car, shopping) (Jones et al. 2003, Walsh et al. 1998) and this severely limits independence and quality of life. In addition to interfering with rehabilitation, postoperative pain can become chronic pain if uncontrolled, (Capdevila et al. 1999, Peters et al. 2007, Puolakka et al. 2010, Sinatra 2010) which is moderate to severe in up to 35% of patients (Brander et al. 2003, Visser 2006, Callahan et al. 1994, Wylde et al. 2011, Peng et al. 2014).

Present treatments for postoperative TKA pain are ineffective, carry risks of side effects/complications, and/or are not indicated for extended use.

Following TKA, patients are given various treatments to relieve postoperative pain. The most common treatment strategy is multimodal pain management, consisting of various medications (analgesics) used in combination with regional nerve blocks.

Analgesics: Although analgesics are used both in-hospital and in the home environment after discharge, their risks of side effects and dependence make them undesirable. The primary analgesics used in multimodal pain therapy are opioids (*e.g.,* oxycontin), which carry risks of dependence and debilitating side effects that cause substantial discomfort and interfere with physical rehabilitation (*e.g.,* sedation, dizziness, nausea, gastrointestinal problems, sleeping problems) (Sinatra 2010, Strassels et al. 2005, Apfelbaum et al. 2003, Wheeler et al. 2002, Kastanias et al. 2010, Benyamin et al. 2008, Eisenberg et al. 2005). Anticonvulsants (*e.g.,* gabapentin, pregabalin) are also used in multimodal pain therapy (Andersen et al. 2009, Buvanendran et al. 2010, Clarke et al 2009) but also carry risks of side effects (sedation, dizziness, headache, blurred vision) that limit physical rehabilitation (Buvanendran et al. 2010, Clarke et al 2009, Zhang et al. 2011). Other non-opiates (NSAIDs, acetaminophen) have minimal risk of side effects but are insufficient on their own and are most often paired with other analgesics. Fear of pain medications and addiction is one of the top concerns of patients prior to TKA (Chang et al.

2004). [redacted]

Regional nerve blocks: Single shot (*i.e.,* injection) and continuous blocks (*i.e.,* using a catheter) can provide relief of postoperative pain while recovering from surgery in the hospital, but they are not suitable for extended use outside the hospital. Blocks targeting mixed nerve trunks (*i.e.,* femoral, sciatic, "3-in-1") can inhibit motor function in the lower limbs, impeding physical rehabilitation and increasing the risk of falls. Alternative approaches can avoid motor block (*i.e.,* adductor canal block, periarticular/intraarticular block) and are useful in-hospital but cannot be practically or safely delivered in the home environment. The analgesic effects of injections last for ≤48 hours and cannot be delivered outside the clinical setting. Continuous nerve blocks are seldom used for more than 7 days due to the risk of infection from indwelling catheters.

Single injections (intrarticular injections of the knee, or injections of the femoral nerve, sciatic nerves, and/or their branches) are short lasting (2 – 48 hours), and can lead to block of normal motor and/or sensory function. It is often challenging to administer adequate anesthesia that provides a sufficient sensory block without impairment of muscle function. If motor/sensory block occurs, then rehabilitation is typically delayed until the effects wear off since the patient is at greater risk of falling. Epidural anesthesia can be used to relieve postoperative pain but carries risks of various side effects: epidural bleeding, diminished muscle control, urinary retention, nerve damage, gluteal compartment syndrome, spinal headache, neurogenic bladder, hypotension, respiratory depression, pulmonary hypertension, cardiac decompensation, and risk of spinal infection (Busch *et al.* 2006; Vendittoli *et al.* 2006). Continuous nerve block of the femoral nerve, sciatic nerves, and/or their branches is a treatment where a catheter is placed percutaneously and delivers anesthetic continuously to the peripheral nerves. Although this treatment can reduce acute postoperative pain, there are several risks that limit its use. The risk of infection is a great concern for any TKA treatment but particularly during continuous nerve block. A previous study reported that after 48 hours of Continuous Femoral Nerve Block, 118 (57%) of 208 catheters had positive bacterial colonization. Only 3 of the 118 incidents of colonization (2.5%) resulted in infection (fever, bacteremia), which resolved with removal of the catheter and without antibiotics (Cuvillon *et al.* 2001). However, the rate of infection likely would have been higher had the catheters been left in for longer than 48 hours. Another risk of continuous nerve blocks is impaired motor and sensory function. Because of the concern that nerve block may cause falls during rehabilitation, and rehabilitation is essential to the recovery of normal functioning, continuous nerve blocks are discontinued after a few days to enable the patient to move about. However, pain intensity is greater during movement than during rest (Singelyn *et al.* 1998; Reuben *et al.* 2008; Andersen *et al.* 2009; Fu *et al.* 2009; Lee *et al.* 2011), leaving patients without this option.

Transcutaneous electrical nerve stimulation (TENS): TENS has been investigated as a method of relieving postoperative pain. Although TENS is a widely accepted method of relieving chronic pain, there is limited evidence that it is effective at relieving postoperative pain. When delivered at a sufficient frequency and amplitude, TENS has reduced postoperative pain (Bjordal *et al.* 2003). However, stimulation intensity during TENS is often limited due to the activation of cutaneous nerve fibers, which can cause discomfort and irritation. Because stimulation intensity is limited during TENS, the therapy delivered may be suboptimal.

The proposed non-narcotic therapy may reduce postoperative pain with minimal risk of infection and falls

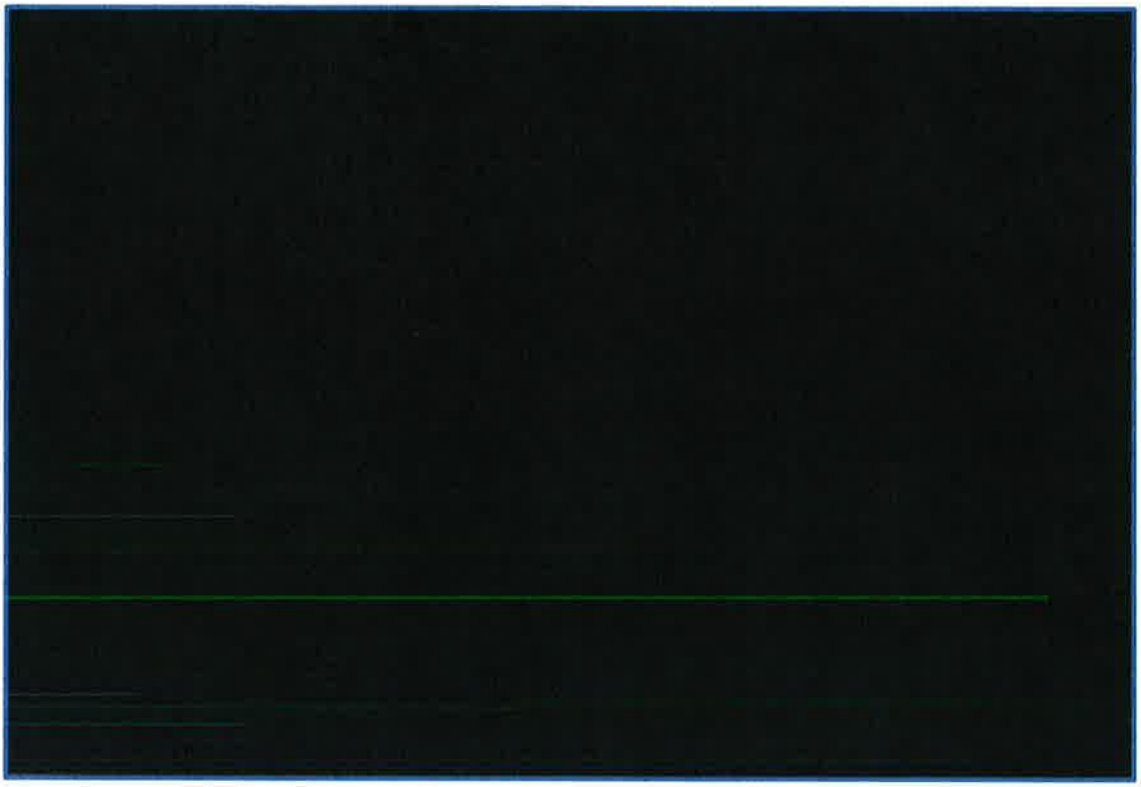
The proposed method aims to relieve postoperative pain following TKA by delivering electrical stimulation through percutaneous fine wire Smartpatch MicroLeads connected to an external pulse generator to target the [redacted] nerves. Unlike TENS, the leads are placed [redacted] and can stimulate the target nerves without cutaneous discomfort. [redacted] Also, compared to the catheters used in continuous nerve blocks, data suggests that the leads pose less of a risk of infection. Also, previous studies indicate that [redacted] are not expected to impair motor and sensory function (see Section 11), which may enable the patient to achieve rehabilitation goals sooner and with less pain.

The proposed therapy may provide immediate pain relief following TKA that can be delivered for several weeks as patients continue their postsurgical recovery

The proposed method may provide immediate pain relief as soon as stimulation is started. PNS also allows for consistent pain relief as stimulation can be provided up to 24 hours per day. Conversely, standard of care treatments typically have a pre-set duration in which pain relief lasts before another dose or therapy must be initiated. The proposed method also will provide stimulation for up to 8 weeks post lead placement, allowing patients access to non-narcotic pain relief throughout their hospitalization, discharge, and rehabilitation.

The proposed method has been successfully used to [redacted] reduce chronic pain in patients with lower limb amputations

The proposed method to treat postoperative pain following TKA has been tested as a treatment for chronic pain in individuals with lower limb amputations. [redacted]



The proposed method has been tested to treat pain in patients following TKA in a separate preliminary study.

Three subjects with pain following TKA (range: postoperative day 6-9) were tested with the proposed approach in a non-significant risk case series study.

Summary

Postoperative pain is a substantial problem for a majority of patients following total knee arthroplasty. Present treatments for postoperative pain during the subacute phase (4 – 30 days following surgery) are ineffective, carry risks of side effects/complications, and/or are not indicated for extended use. The proposed therapy using percutaneous electrical stimulation is expected to reduce postoperative pain and address the shortcomings of existing therapies. The proposed study will determine if this therapy can produce clinically significant reductions in postoperative pain following TKA as compared to historical controls (e.g., published data).

3.0 STUDY OUTCOMES AND EXPLORATORY MEASURES

3.1 Overview

Outcomes and exploratory measures will be collected before and after TKA surgery (see Appendix A for schedule) and include

1. Numerical rating scales for pain intensity: Average Pain while walking (Question 5 of the Brief Pain Inventory-Short Form; BPI-5)
2. Numerical rating scales for pain intensity: Average Pain and Average Pain at rest (Question 5 of the Brief Pain Inventory-Short Form; BPI-5)
3. Cumulative analgesic usage
4. Opioid related side effects (*e.g.,* nausea and vomiting, constipation, urinary retention, pruritis, drowsiness, respiratory depression)
5. Range of Motion (knee flexion and extension angle)
    a. Number of days to achieve key milestones in affected knee (*e.g.,* 90 degree flexion)
    b. Pain "right now" scores before, during, and after ROM testing
6. Timed Up and Go (TUG) test
7. Six Minute Walk Test
8. Fixed Distance Walk Test
9. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
10. Numerical rating scales for pain intensity: Pain Interference (Question 9 of the Brief Pain Inventory-Short Form; BPI-9)
11. Patient Global Impression of Change (PGIC)
12. Pain Catastrophizing Scale (PCS)
13. Time to meet recovery milestones
14. Subject satisfaction survey
15. Subject-shaded diagrams of pain and paresthesia
16. Clinician satisfaction survey

3.2 Primary Outcome

The primary outcome of this study will be the average daily pain while walking over the first 4 weeks following TKA surgery. This will be recorded using Question 5 of the Brief Pain Inventory Short Form (BPI-5; details of BPI below), which assesses "Average Pain" on an 11 point numerical rating scale, with one end representing "No pain" (0) and the other end representing "Pain as bad as you can imagine" (10). Subjects will record BPI-5 scores daily in a diary, and the mean score over the first 4 weeks following TKA will be calculated for each subject. The primary outcome will be compared to historical controls (*e.g.,* published data).

3.3 Secondary Outcomes

Secondary outcome measures will provide additional information on pain and function, which will be used to aid in the design of future clinical studies.

Brief Pain Inventory-Short Form (BPI)

The BPI is a widely used assessment designed to measure pain intensity and the interference of pain on daily activities and moods (Cleeland and Ryan 1994). The BPI is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) panel and has demonstrated validity and reliability across many cultures and languages (Cleeland and

Ryan 1994; Tan et al. 2004; Dworkin et al. 2005). The IMMPACT panel was assembled to develop consensus recommendations to improve and standardize the design and conduct of clinical trials involving treatments for pain. [redacted]

Cumulative Analgesic usage

The amount and type of analgesic used by the subject will be recorded daily in a diary before TKA surgery, from the subject's records during their hospital stay, in daily diaries after discharge from the hospital, and at each visit following End of Treatment. Specific analgesic information that will be collected may include Patient Controlled Analgesia (PCA) dosage requests, PCA dosage, intravenous (IV) medications (opioids and non-opioids), oral opioids, and oral non-opioid pain medications. This information will provide an indirect measure of pain intensity, as usage of analgesics may relate to the amount of pain experienced. Narcotic usage may be converted into a morphine equivalent dosage (MED). The use of other methods of pain relief will also be recorded (*e.g.,* cryotherapy).

Opioid Related Side Effects

Opioid pain medications are associated with a wide variety of side effects. Common side effects include nausea and vomiting, constipation, urinary retention, pruritis, drowsiness, and respiratory depression. Subjects may be questioned for each of these side effects throughout the study. Side effects from narcotic therapy will be collected but not reported as adverse events.

Range of motion

Adequate knee ROM is essential for activities of daily living but is limited by postoperative pain.. The active ROM (AROM; no assistance from clinical staff) and passive ROM (PROM; assisted by clinical staff) will be assessed during the study, and when possible the same clinical staff members at each site should take all ROM measurements to limit intertester variability. [redacted]

[redacted] Pain may be assessed before, during, and/or after ROM measurements (*e.g.,* at maximum flexion, at maximum extension) using Question 6 of the Brief Pain Inventory-Short Form (BPI-6). BPI-6 rates "Pain right now" on an 11 point numerical rating scale, with one end representing "No pain" (0) and the other end representing "Pain as bad as you can imagine" (10).

Timed Up and Go (TUG) Test

The TUG test is an objective measure of mobility. The subject begins by sitting in a standard chair (*e.g.,* uncushioned chair with armrests and seat height of 46 cm). A line is placed on the floor approximately ten feet (*i.e.,* 3 meters) away. The subject is timed while they stand up, walk to the line at a normal, safe pace, walk back to the chair, and sit down. The test is reliable, a good indicator of the patient's recovery from TKA, and easy to complete. The TUG test will be completed at various time points, including: the baseline visit (Visit 1), once during the in-hospital treatment visits, such as the anticipated last visit before discharge (when deemed safe by clinical staff), and during visits following hospital discharge. Regular footwear should be worn, and the use of any assistive devices (*e.g.,* canes, walkers) is permitted and will be recorded.

Six minute walk test (6MWT)

The 6MWT records the total distance the subject can walk in 6 minutes. It is frequently used to measure endurance and is validated as a measure of mobility following TKA. Assistive devices (*e.g.,* canes, walkers) may be used during the 6MWT. If the 6MWT can be conducted, then the total distance walked is recorded (subjects unable to walk at all will receive a score of 0 meters). Subjects will be allowed to rest during the test if necessary. The 6MWT may be administered at Visit 1 (before TKA surgery) and at visits following hospital discharge.

Fixed distance walking test
Subjects may be asked to walk a fixed distance (*e.g.,* 20 meters) with or without an assistive device or help from clinical staff, and the time required to walk this distance may be measured to assess walking speed. Also, the first day following TKA surgery at which the subject can walk specific distances (*e.g.,* 20 meters) may be recorded. The test may be administered at Visit 1 and once during the in-hospital treatment visits, such as the anticipated last visit before discharge (when deemed safe by clinical staff).

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
The WOMAC is a widely-used validated questionnaire to evaluate patients with osteoarthritis of the knee and consists of 24 items evaluating pain (5 items), stiffness (2 items), and physical functional disability (17 items) (Bellamy *et al.* 1988). Each item is scored on an 11 point numerical rating scale from 0-10, and greater scores indicate worse pain, stiffness, and functional disability. The WOMAC may be administered at Visit 1, during in-hospital visits, and during visits following hospital discharge. Also, WOMAC scores from before the TKA procedure may be collected from medical charts, if available.

Patient Global Impression of Change (PGIC)
Participant ratings of global improvement are one of the core outcome domains in chronic pain studies (Dworkin *et al.* 2005). The Patient Global Impression of Change (PGIC) Scale will be administered during in-hospital treatment visits and at visits following hospital discharge to assess subject perception of overall improvement (Guy 1976). The PGIC Scale asks subjects to rate their improvement with treatment on a 7-point scale that ranges from "very much worse" to "very much improved". The scale provides subjects the opportunity to combine all of the components of their experience into one overall measure and allows clinicians to assess the clinical significance of each subject's improvement or worsening over the course of the study.

Pain Catastrophizing Scale (PCS)
The PCS is a widely-used, validated and reliable 13-question instrument to assess rumination (4 questions), magnification (3 questions), and helplessness (6 questions) (Sullivan, 2009.; Osman *et al.* 1997). The survey asks participants to think back on painful experiences in the past and reflect on how often they had specific thoughts or feelings. Each question is scored on a 0-4 scale with 0 = "not at all" and 4 = "all the time". Higher scores indicate a greater tendency towards catastrophizing pain, which has been correlated with worse postoperative pain and response to pain therapies (Riddle et al 2010; Pavlin et al 2005; Forsythe et al 2008). The PCS may be assessed at Visit, 1 the EOT visit and at the three-month follow-up visit.

Time to Meet Recovery Milestones
Discharge criteria differ between hospitals, but may include the following: 1) patient is medically stable, 2) pain controlled without nerve block (*i.e.,* single shot or continuous regional/neuraxial nerve blocks), 3) patient able to walk 30 meters ensuring Activities of Daily Living can be completed at home, and 4) patient can walk a set number of stairs (e.g., half a flight). The time until the subject meets criteria related to hospital discharge will be measured. Also, the subject's length of stay in the hospital following TKA will be recorded (number of days and/or hours), as well as discharge destination (*e.g.,* home, acute inpatient rehabilitation, skilled nursing facility). In

addition, the time required to reach other important recovery milestones may be measured, such as 1) walking with assistive device (*e.g.,* cane, quad stick, walker), 2) walking without assistive device, 3) return to work, and 4) cessation of narcotic usage.

Subject satisfaction survey
A survey will be administered to the subjects at study intervals to assess their satisfaction with the study and postsurgical pain therapies.

3.4 Exploratory Measures

Analyses of primary and secondary endpoints at other study intervals
The primary and secondary endpoints may be assessed at other study intervals not listed above.

Subject-shaded diagrams of pain [redacted]
Subject-shaded diagrams are a common tool for the diagnosis of pain. [redacted]

Clinician satisfaction survey
A sponsor-developed Clinician Satisfaction Survey will be administered. This survey will be administered to the site personnel primarily completing device programming at each site and includes questions pertaining to use of the Sprint system as well as the overall impression of the therapy. This survey will be administered at the conclusion of the study enrollment for that particular clinical center and may be administered sooner as needed.

3.5 Safety Endpoint

The primary safety endpoint is the occurrence of device related adverse events. All adverse events (AEs) that occur during the study will be documented. Specific details regarding any observed AE will be collected on an Adverse Event Form and will be followed to resolution. Adverse Events will be tabulated and summarized at the conclusion of the study.

4.0 Device Description

4.1 Overview

During lead placement, test needles connected to either the Sprint Stimulator (Section 4.4), or the Sprint Test Stimulator (Section 4.7), may be used to apply electrical stimulation to peripheral nerves in the lower limb to determine appropriate electrode location and stimulation parameters. [redacted] Each subject will receive up to two leads, which will be connected to up to two Sprint stimulators (*i.e.,* one lead per stimulator).

The key components of the Sprint PNS System are shown in Figure 3 and include:

Non-sterile single use disposable components for use by a single subject

- **Sprint Stimulator** [redacted]
2. **Sprint Pad** [redacted]
- **Smartpatch Cable** [redacted]
- **Smartpatch Lead Connector Tape** [redacted]
- **Alligator Clip Cable** [redacted]
- **Sprint Stimulator Battery** [redacted]
- **Sprint Test Stimulator Battery (** [redacted]
- **Sprint Belt** [redacted]

Sterile, single-use disposable components for use on a single subject

- **Smartpatch MicroLead™ and Introducer** [redacted]
- **Smartpatch Lead Connector and Wrench** [redacted]
- **Smartpatch Test Cable** [redacted]
- **Smartpatch Test Needle** [redacted]

Non-sterile component for use by multiple subjects:

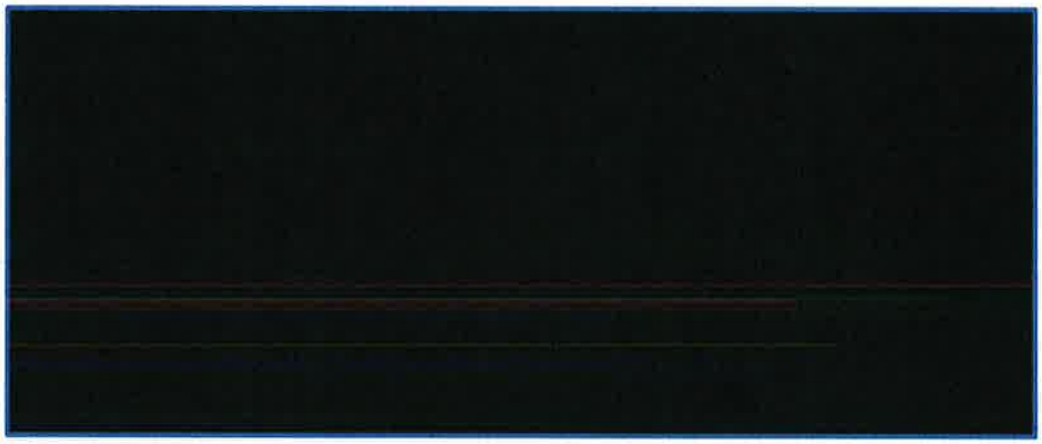
[redacted] **Sprint Test Stimulator** [redacted]

[redacted]

4.2 Smartpatch MicroLead™ and Introducer

[redacted]

[redacted]

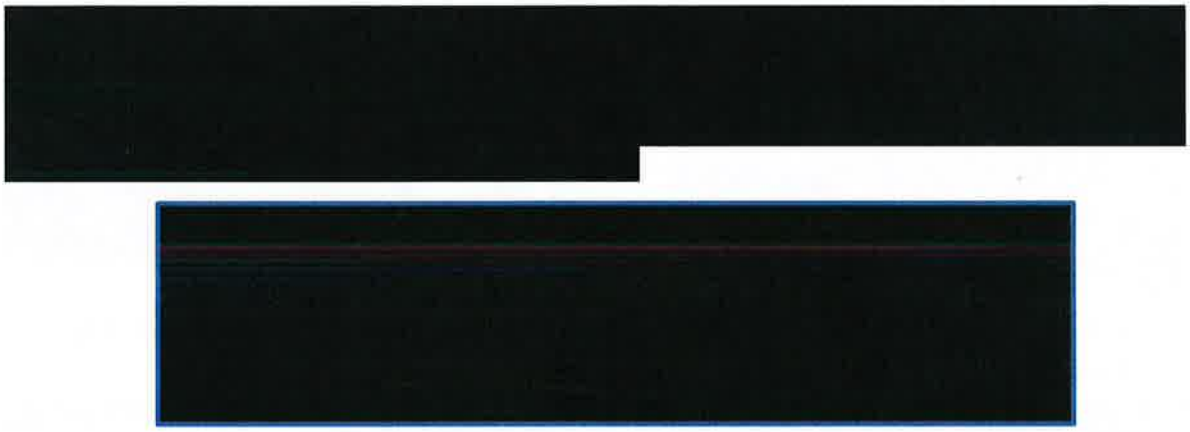


4.3 Smartpatch Lead Connector, torque wrench, and Lead Connector Tape

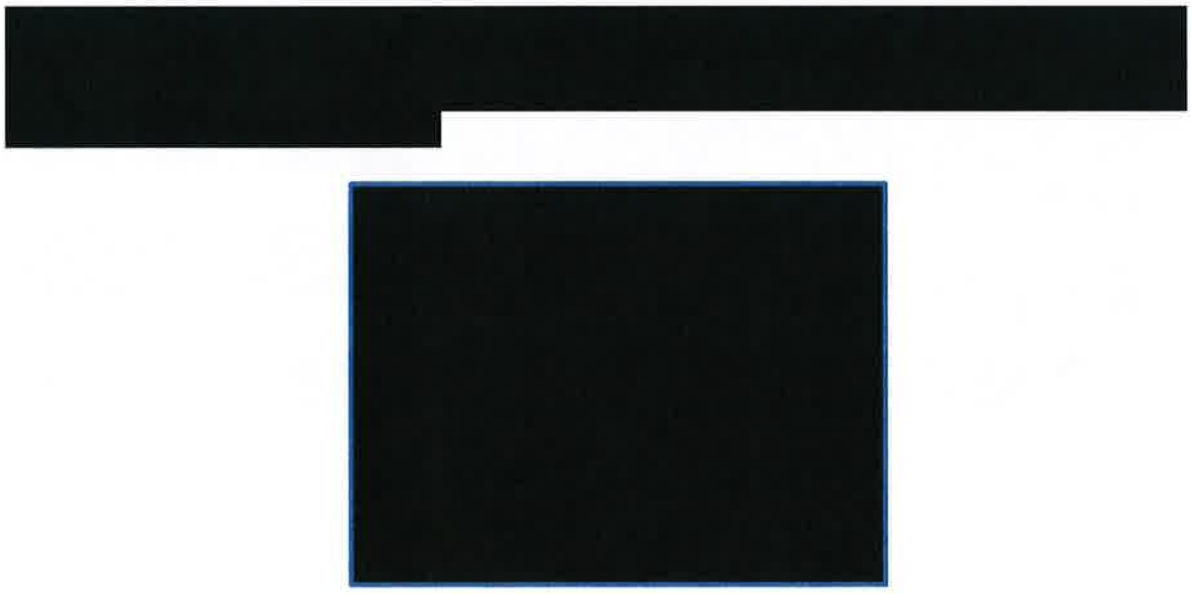
[redacted]

4.4 Sprint Stimulator and Sprint Pad

4.5 Smartpatch Cable



4.6 Smartpatch Test Needle



4.7 Sprint Test Stimulator

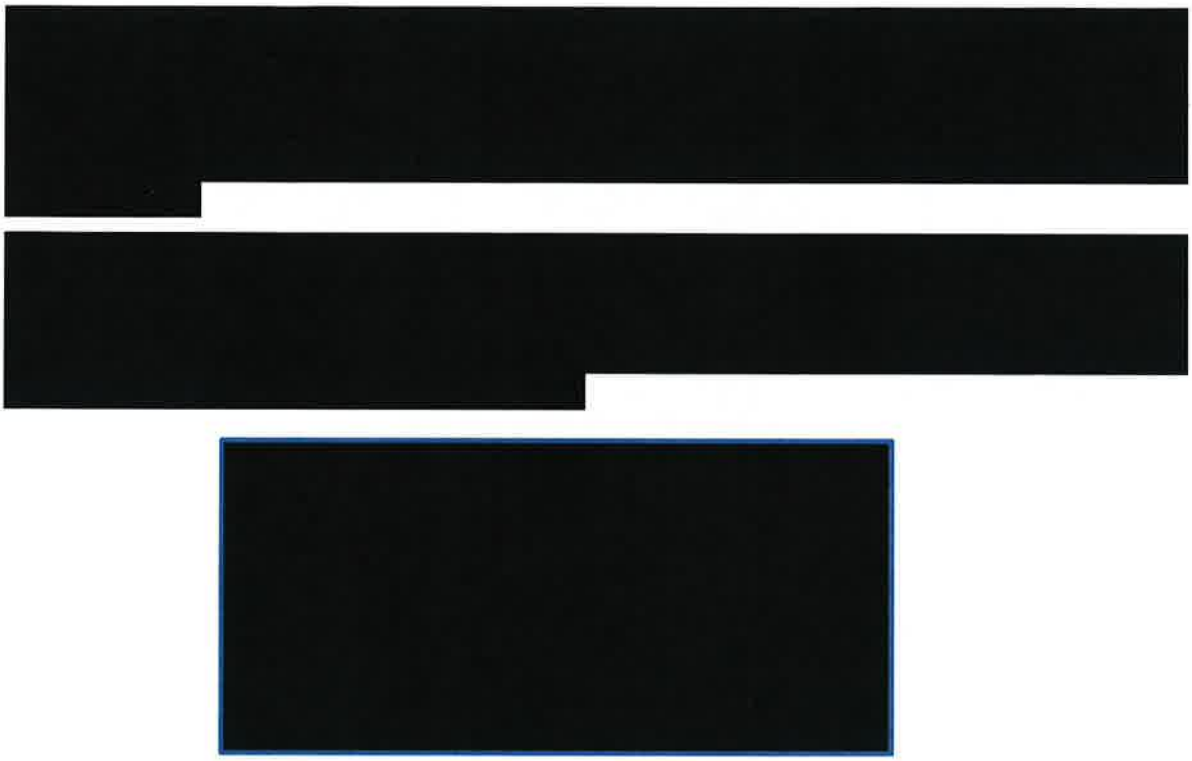
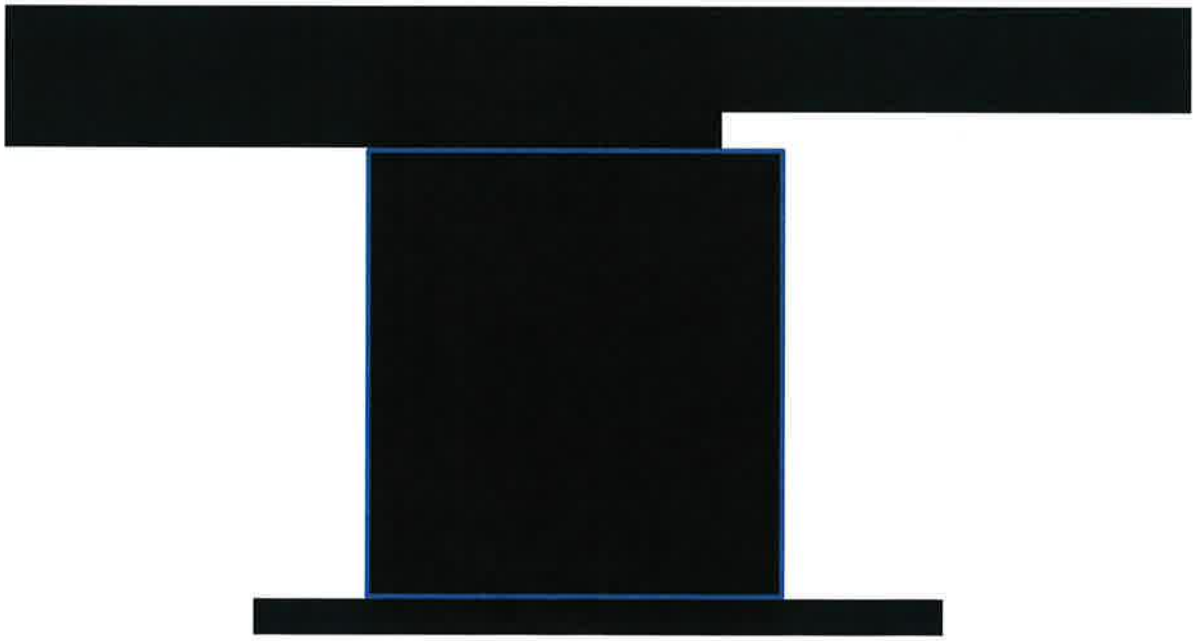
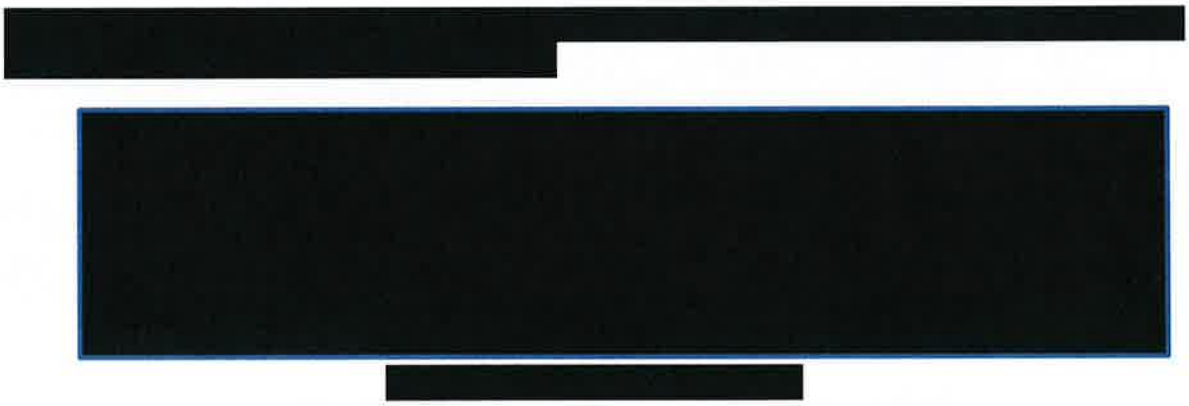


Figure 9: Sprint Test Stimulator

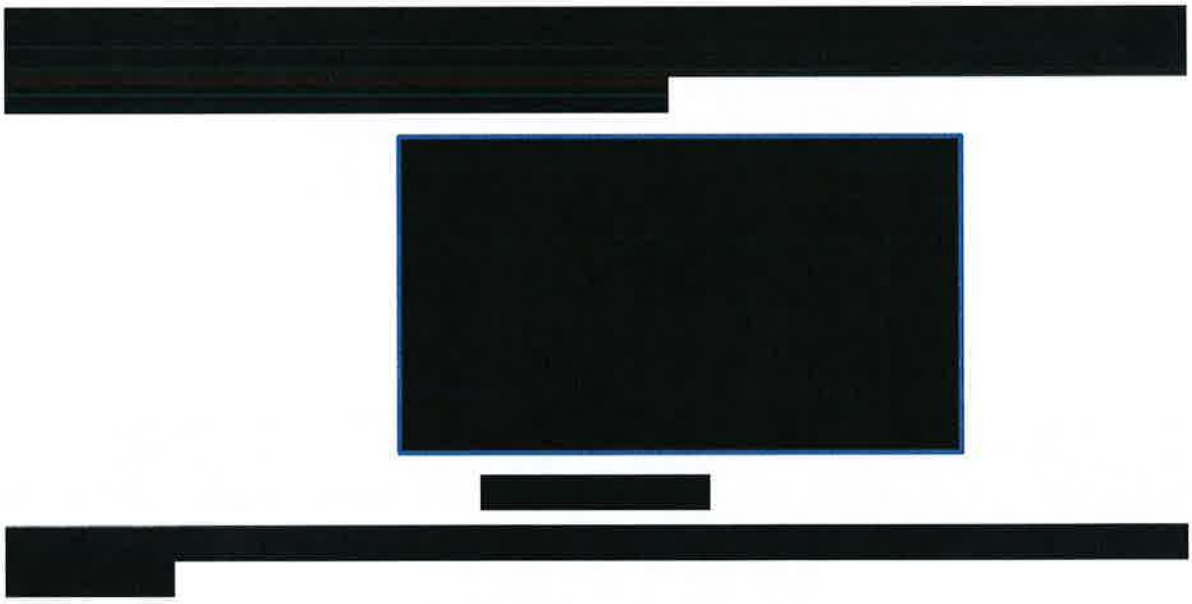
4.8 Alligator Clip Cable



4.9 Smartpatch Test Cable



4.10 Battery



4.11 Sprint Belt

4.12 Accessories

[redacted]

5.0 SCOPE

5.1 NUMBER OF SITES
Up to 6 investigational sites.

5.2 NUMBER OF SUBJECTS
Up to 36 subjects will be enrolled in the study. Enrolled subjects are those that undergo procedures associated with lead placement. All enrolled subjects will receive a Subject ID number. The number of subjects to be enrolled does not include subjects who do not meet all of the eligibility criteria or who do not undergo procedures associated with lead placement.

6.0 STUDY PROTOCOL

6.1 Overview
This study is a prospective case series study to determine the treatment effect of Peripheral Nerve Stimulation (PNS) therapy for the treatment of knee pain following Total Knee Arthoplasty (TKA) utilizing preoperative lead placement.

6.2 Study Population
Prospective subjects will be screened for eligibility into the study from the available pool of candidates who are scheduled to undergo a primary unilateral TKA. Subjects will be screened using the Eligibility criteria listed in section 6.3. Recruitment materials will be provided to aid in subject enrollment. All recruitment materials will be IRB approved prior to their use.

6.3 Eligibility

6.3.1 Inclusion Criteria

1. At least 21 years old
2. Scheduled to undergo a primary unilateral total knee replacement procedure
3. Able to understand and willing to take part in study and comply with all study requirements

6.3.2 Exclusion Criteria

1. Body Mass Index (BMI) > 40 kg/m^2
2. [redacted]Compromised immune system based on medical history[redacted]
3. History of valvular heart disease
4. Implanted cardiac pacemaker/defibrillator or Deep Brain Stimulator
5. Evidence of joint or overlying skin infection of the affected limb

6. History of recurrent skin infections
7. Bleeding disorder **OR** INR ≥ 1.5 for those on warfarin
[redacted] Confounding conditions [redacted]
[redacted] History of nerve damage in the affected lower limb [redacted]
10. Allergy to skin surface electrodes and/or medical-grade adhesive tapes
11. Allergy to all local anesthetic agents such as lidocaine or previous reaction to anesthesia
12. Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator
13. Prisoners, minors, legally incompetent people, unconscious patients, house staff, or students
14. Pregnant
15. History of substance abuse within 6 months
[redacted] Potential secondary gain issues [redacted]

6.4 Concurrent Medications and Non-Drug Therapies

Subjects will be permitted to use analgesic medications (opioid or non-opioid) as prescribed/recommended by their physician and analgesic usage will be recorded. For surgical anesthesia, subjects will not be allowed to receive any blocks in the upper thigh/buttocks (e.g., single injection or continuous blocks of the femoral or sciatic nerves) or blocks in any location using long lasting agents (e.g., liposomal Bupivacaine, or Exparel). Postoperatively, subjects will not be allowed to receive continuous regional nerve blocks. Subjects will also not be allowed to use other electrical stimulation therapies (*e.g.,* transcutaneous electrical nerve stimulation [TENS] or neuromuscular electrical stimulation [NMES]) throughout the study. Additionally, any rehabilitation activities that may conflict with the device Instructions for Use (such as swimming or water therapy) should not be performed until after end of therapy. All interventions targeting pain control will be recorded on the appropriate pages of the Case Report Form (CRF).

6.5 Study Plan

The study procedures for this protocol are classified according to the following time periods: Consent; Lead Placement and Testing; Start of Treatment; In-Hospital Treatment; Post-Discharge Treatment; and Follow-up. Appendix A provides a schedule of the study procedures.

[redacted]

6.5.1 Visit 1 - Consent

Subjects will receive a detailed explanation of study specific procedures as well as the risks and benefits of participating in the study. The subject will be asked to sign the approved study consent during this visit. If the subject agrees to participate by signing the consent form, all inclusion/exclusion criteria will be verified by completing the eligibility form and then all baseline information will be collected and recorded on the appropriate case report form (CRF).

[redacted]

The subject's most recent pre-operative measurements of Range of Motion (ROM) may be documented, if available. The following outcome measures may be assessed:

- BPI-5 ("Average pain") standard, at rest, and while walking
- Fixed Distance Walk test
- TUG test
- Six Minute Walk test
- BPI-9 (Pain Interference)
- WOMAC
- Pain Catastrophizing Scale (PCS)
- Current pain treatments and analgesic usage
- Assessment for opioid related side effects

If needed due to time constraints, any of the above outcome measures may instead be performed at Visit 2. Women of childbearing age will have a pregnancy test completed as part of eligibility confirmation before or at Visit 2.

6.5.2 Visit 2 – Lead Placement and Testing

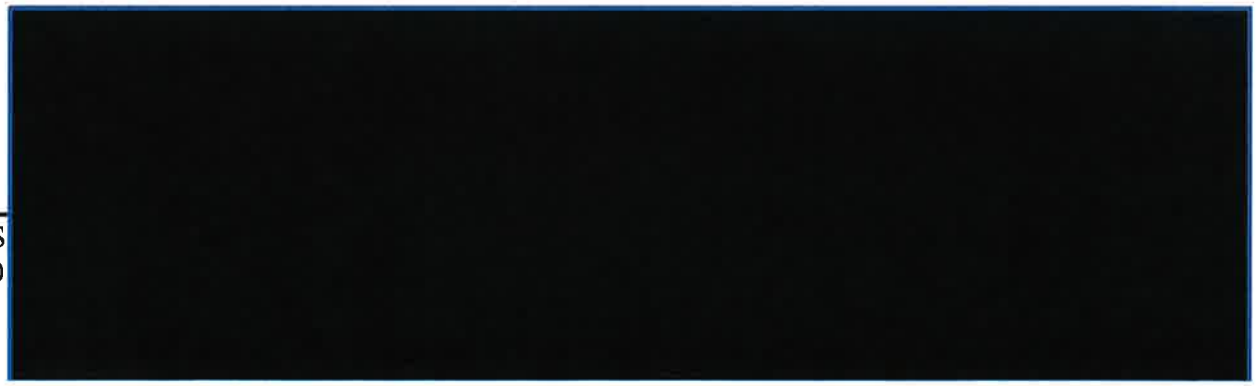
Following the consent visit, participants who meet all eligibility criteria will undergo placement of the percutaneous Smartpatch MicroLeads. Visits 1 and 2 may be performed on the same day. As a safety precaution to prevent potential excessive bleeding, subjects on warfarin will have blood drawn to confirm an INR of < 1.5. If the INR is not below 1.5, subjects will be given the opportunity to have their warfarin dosage adjusted and the INR will be retested up to two additional times. The INR must be collected within 48 hours prior to the Lead Placement and Testing (Visit 2).

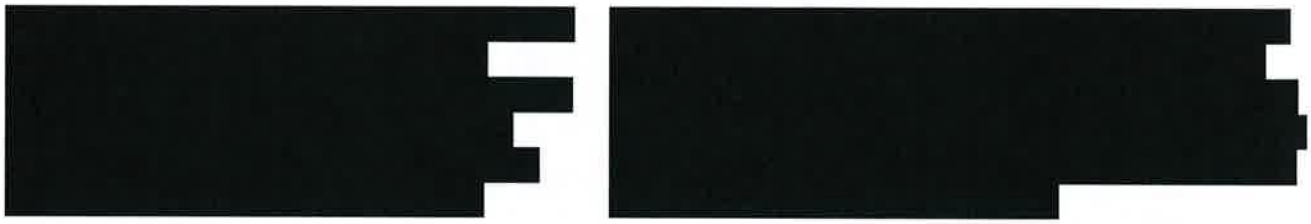
The following outcome measures may be assessed prior to lead placement:

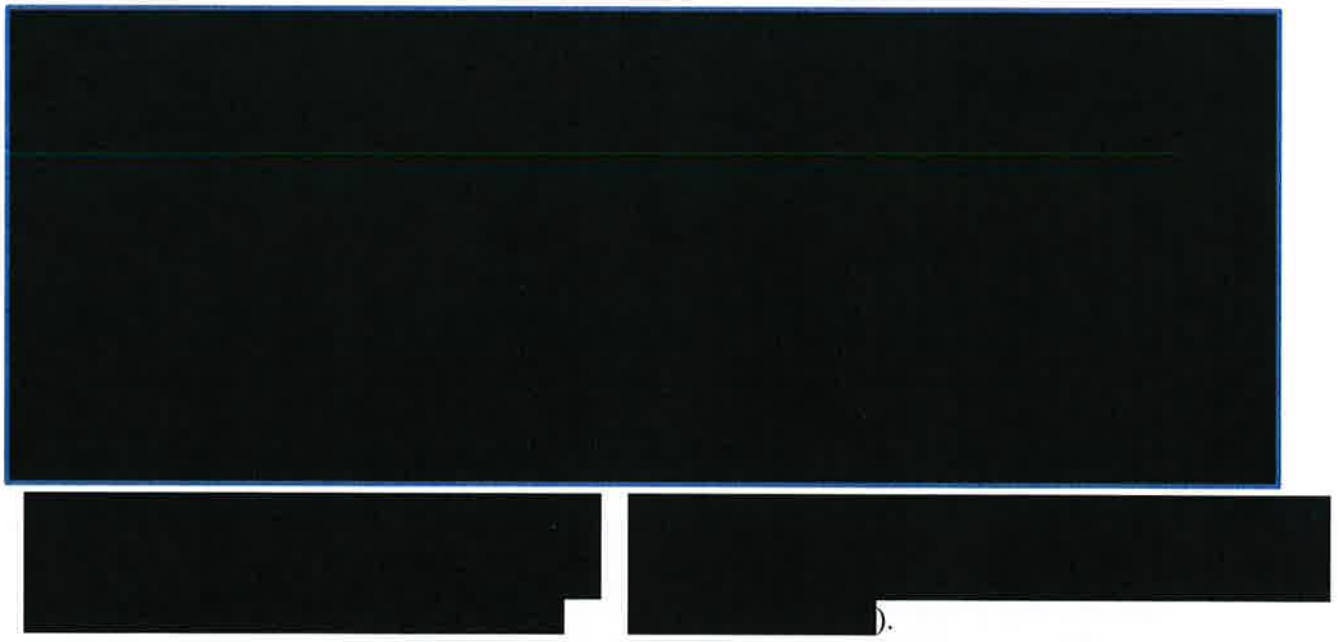
- Subject-shaded leg pain diagram
- Current pain treatments/analgesic usage
- Opioid-related side effects
- ROM (knee flexion and extension) and pain during ROM (pre-lead placement ROMs optional)

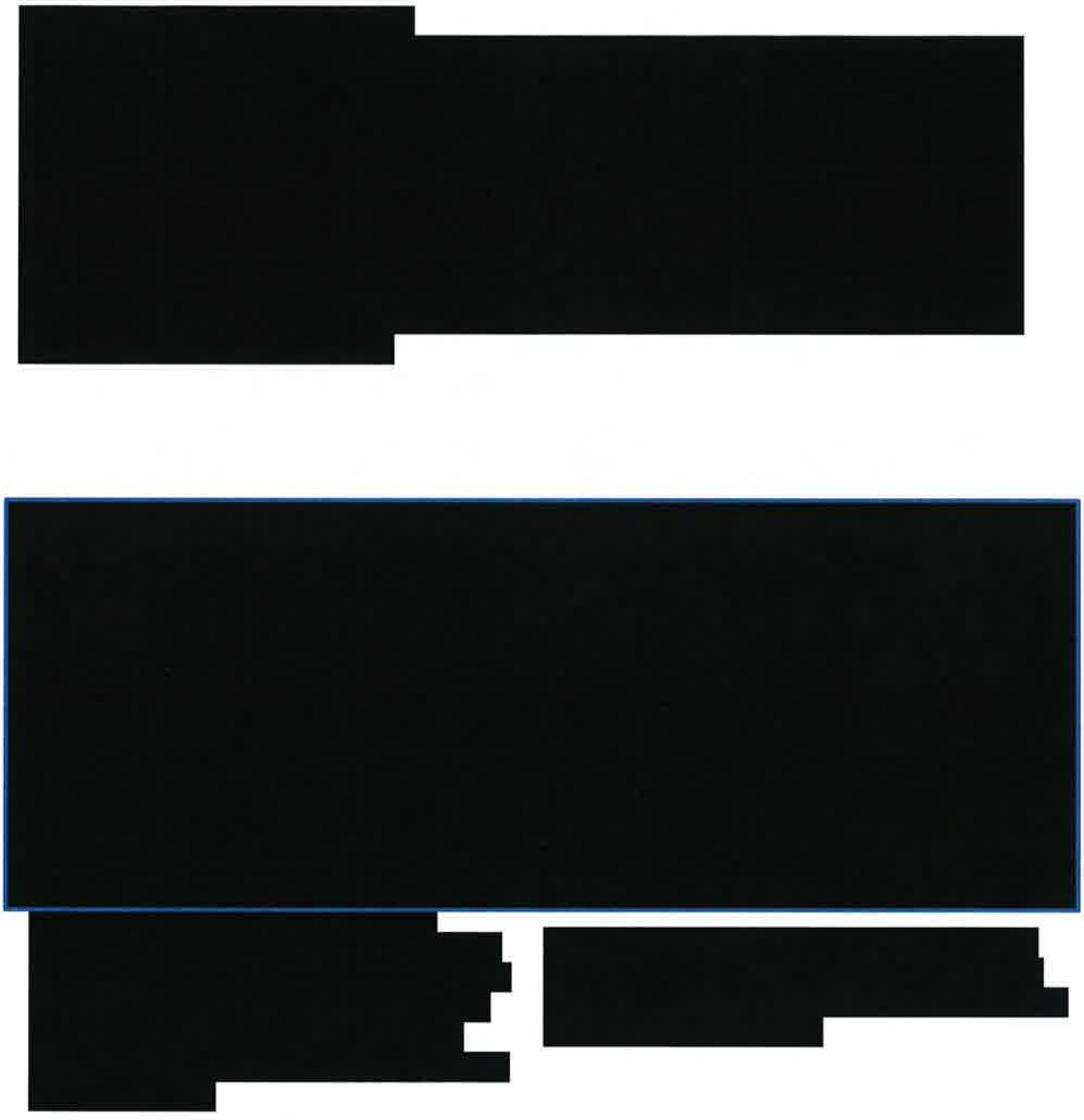
[redacted]

[redacted]









[redacted]

Determination of stimulation parameters:
Stimulus parameters will be varied over a range of parameters [redacted]

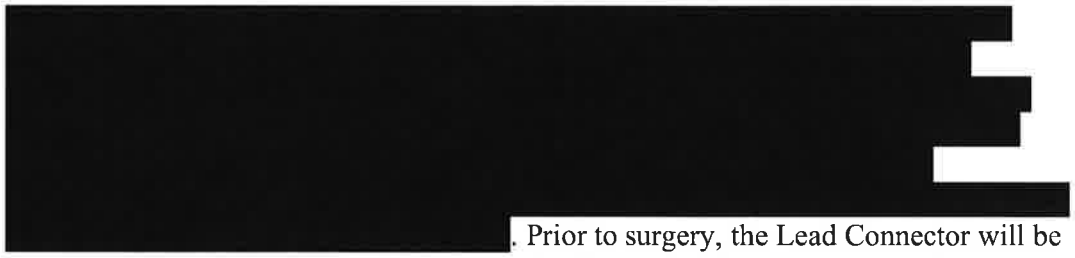
Following lead placement, the following outcome measures may be assessed:

- ROM (knee flexion and extension) and pain during ROM
- Subject-shaded diagram of paresthesia coverage of leg

This study has a large number of stimulus parameters and ranges to investigate. It is possible that the optimal stimulus parameters may not be determined during this Visit. Thus, at the conclusion of this Visit a subject will

a. Proceed to treatment phase:

(i) Subjects with acceptable lead placement and stimulation parameters will be prepared to proceed to the treatment phase. Stimulation may be delivered up to the time of the TKA, provided the lead placement occurs more than 2 days prior to the TKA. The subject will be educated on the use of the system as noted in Section 6.6.3. Subjects receiving preoperative stimulation may complete the daily diary on each day stimulation is received as well as the PGIC and WOMAC on the last day of the diary.



. Prior to surgery, the Lead Connector will be disconnected from the Smartpatch Cable and stimulator. The lead and lead connector will be secured beneath sterile, waterproof bandages (Tegaderm by 3M, Nexcare, or equivalent) and worn until completion of the TKA surgery. Following TKA, all subjects will use the stimulation system to determine if stimulation can provide pain relief. OR

b. Return for another Visit 2:

(i) 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 OR

c. Terminate from the Study:

(i) 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 a 24-48 hour telephone follow-up. If an AE is noted, the subject will be followed until the AE resolves.

Additionally, the site must ensure the subject does not have the lead for greater than 60 days (*i.e.,* if the subject received the lead 14 days prior to TKA, the site must schedule their End of Treatment visit so it is no later than 60 days after lead placement).

Data regarding the specific details of the lead placement procedure will be collected during this visit and recorded on the appropriate Case Report Form. Images (*e.g.,* photographic, video, ultrasound) may be collected to provide a visual record of the locations of electrodes/leads and anatomy. Subject consent will be obtained for photography or video recording, and subjects will be de-identified in photos or videos.

6.5.3 Telephone Follow-Up (Visit 3)

All subjects will receive a Telephone Follow-up 24 - 48 hours after each Visit 2 (Lead Placement) to query for any adverse events. All AEs will be followed until resolution. Subjects

who return for Visit 2 but do not undergo lead placement will not receive a follow-up phone call to assess adverse events because they will not have participated in the lead placement procedure.

6.5.4 Day of TKA and Start of Stimulation following TKA (Visit 4)

Following TKA surgery, the bandages covering the leads will be carefully removed and the leads will be connected to the Stimulators. Stimulation will be delivered to determine if postoperative pain can be reduced. [redacted] Stimulation will be delivered for up to approximately 24 hours/day (except when bathing, changing the battery, etc.) until end of therapy (*i.e.,* approximately 6 weeks following TKA surgery. Leads will be indwelling for no more than 60 days total). Additionally, Visits 1, 2 and 4 may occur on the same day, such as the day of the TKA (if so, visit 3 is not required).

Stimulation parameters may be varied. [redacted] The care and maintenance of the stimulation system, leads, and lead exit sites will be performed by members of the clinical or study staff. Subjects will also be provided with a manual and instructed on the use and care of the device in case changes are required when clinical/study staff is not present.

Sterile, waterproof covering bandages [redacted] will be placed over the exit sites of the leads. Additional bandages may secure the lead connections. The site may choose to utilize a skin adhesive [redacted] The clinical/study staff and subject will be instructed to inspect the electrode exit site for signs of irritation and report them to the clinician. [redacted] The area around the leads and surface electrodes will be kept clean and dry. If bandages become wet or loose, the bandages will be changed. A bandage change will not be considered an Adverse Event (AE), but may be documented.

The following outcome measures may be assessed during Visit 3:

- [redacted] Patient shaded leg diagrams of pain [redacted]
- Current pain treatments/analgesic usage
- Subjects will be given a diary to record their daily "Average Pain" [redacted] The diary will be completed for each day of treatment.

6.5.5 In-Hospital Treatment: (Visits 5a, b, c, etc.)

On each day of in-hospital treatment (starting at POD 1), clinical/study staff will visit the subject in the subject's unit. If necessary, pads and/or batteries will be replaced and stimulation parameters may be adjusted. [redacted]

[redacted] Maintenance and care of the leads and lead exit sites will be performed, including visual inspection and bandage changes, if necessary.
The following outcome measures may be assessed during each Visit 5:

- [redacted] Pain [redacted]
- [redacted] Completion of daily diary
- Range of motion ([redacted] and pain during ROM
- Fixed Distance Walk Test (only at the anticipated last visit before discharge)
- TUG Test (only at the anticipated last visit before discharge)
- WOMAC (only at the anticipated last visit before discharge)
- [redacted] BPI-9 [redacted]
- Patient Global Impression of Change (PGIC) (only at the anticipated last visit before discharge)
- Time to recovery milestones
- Current pain treatments/analgesic usage
- Assess for opioid-related side effects

In addition, subjects will be queried for adverse events. Outcomes requiring physical function of the subject (such as Fixed Distance Walk Test or TUG Test) must be assessed by the physical therapy staff for the in-hospital visits. All functional outcomes will only be administered if deemed safe by the staff. If it is deemed unsafe to complete a test or if the subject is unable to complete a test, it will not be considered a protocol deviation.

6.5.6 Post-Discharge Treatment: Weeks 1 through 5 after TKA surgery (Visits 6-10)
Visits will occur 1 week (Visit 6), 2 weeks (Visit 7), 3 weeks (Visit 8), 4 weeks (Visit 9), and 5 weeks (Visit 10) after TKA surgery. The 2-week visit will occur in person; all other visits may be completed via telephone. Subjects will be reminded to complete their daily pain diaries. In addition, subjects will be queried for adverse events.
Subjects will continue to be followed regardless of discharge location (home, inpatient rehabilitation facility, outpatient rehabilitation facility). Sites should make every effort to work with outside facilities to ensure the subject can return to the clinic.

The following outcome measures may be assessed during the Visit 6, 8, 9 and 10 telephone calls:

- [redacted] BPI-5 [redacted]
- Pain [redacted]
- BPI-9 [redacted]
- PGIC
- Time to recovery milestones
- Current pain treatments/analgesic usage
- Assess for opioid-related side effects

In addition to the above, the following may be assessed during the Visit 7 in-person evaluation or any other post-discharge treatment visits conducted in person:

- Inspection of bandages and lead exit site
- Adjustment of stimulation parameters (as needed)
- ROM [redacted] and pain during ROM
- Six-Minute Walk Test
- TUG Test

- WOMAC

6.5.7 End of Treatment: 6 weeks after TKA surgery (Visit 11)

The End of Treatment will occur 6 weeks after TKA surgery. The lead must be removed within 60 days of lead placement. Prior to lead removal, additional electrical stimulation testing may be conducted in the clinic. In addition, subjects will be queried for adverse events.

The following outcome measures may be assessed:

- [redacted]BPI-5 [redacted]
- Pain [redacted]
- ROM [redacted] and pain during ROM
- Six-Minute Walk Test
- TUG Test
- WOMAC
- [redacted]BPI-9 [redacted]
- PGIC
- Subject Satisfaction Survey
- PCS
- Time to recovery milestones
- Current pain treatments/analgesic usage
- Assess for opioid-related side effects

At the conclusion of this visit, the leads will be removed [redacted] and will be examined to confirm that they are intact upon removal. The Investigator will perform a visual inspection of the removed leads. If results of the visual inspection are suggestive of a broken lead or retained fragment, a radiograph may be taken to confirm the presence or absence of retained fragment(s). The Investigator will determine what is medically required to further evaluate and treat the subject for the retained fragment.

6.5.8 Follow-up Visits: Visits 12-(2 months), Visit 13 (3months)

Visits will occur at 2 months (Visit 12) and 3 months (Visit 13) after TKA surgery. The 2-month visit may be completed via telephone and the 3-month visit will occur in person. At each visit, subjects will be queried for AEs.

The following outcome measures may be assessed during the Visit 12 telephone call:

- [redacted]BPI-5 ([redacted]
- BPI-9 [redacted]
- PGIC
- Time to recovery milestones
- Current pain treatments/analgesic usage
- Assess for opioid-related side effects

In addition to the above, the following may be assessed during the Visit 13 in-person evaluation:

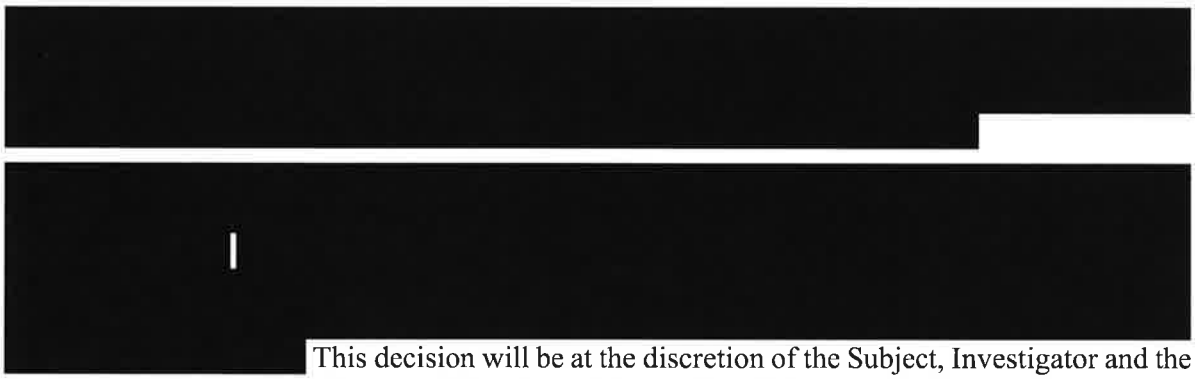
- Inspection of lead exit site
- [redacted]Diagram of pain [redacted]
- ROM [redacted] and pain during ROM
- Six-Minute Walk Test
- TUG Test

- WOMAC
- PCS

In addition, subjects will be queried for adverse events. If no AEs are noted, the subject will be discharged from the study following the 3-month visit. Any AE will be documented, addressed, and followed to resolution.

6.5.9 Unscheduled Visits/Lead Replacements

Subjects may require an unscheduled visit if they experience a technical issue with the stimulation system that the clinical staff has difficulty resolving, desire adjustments to stimulation parameters, require a bandage change or lead replacement, or experience an adverse event which requires further evaluation by the clinical study staff. Communication with the subject for minor issues (*e.g.,* technical issues that can be easily resolved) will not be considered as unscheduled visits, but will be recorded in the Communications Log.



This decision will be at the discretion of the Subject, Investigator and the Sponsor and should take into account the following considerations

1) the subject's desire to continue with the therapy and understanding that the same risks of the initial lead placement would apply again,
2) the Investigator's belief that the intended target location is healthy enough to place another lead and there are no concerns with patient compliance with the care of the lead exit site, and
3) the amount of time remaining in the home trial.

Alternatively, if one lead fails to improve postoperative pain, then the subject may continue using only the effective lead (i.e., one system).

Any additional lead placements will involve additional instances of Visit 2 (described above) and the associated requirements (e.g., subjects who initially required an INR test prior to the first lead placement will have the test repeated as necessary). Subjects will then receive the remaining balance of the stimulation therapy. Subjects will have an additional exposure to the risks of lead placement, but the risks are the same as the risks detailed for the initial procedure (Section 12).

6.6 Study Visit Windows

The acceptable windows for each visit are listed below in **Table 1.**

Table 1 Study Visit Windows

Visit Number	Visit Name	Window
1	Baseline	[redacted]
2	Lead Placement and Testing	
3	Follow-up phone call	[redacted]
4	Day of TKA (POD 0; start of stimulation)	
5a, b, c…	Daily in-hospital visits	[redacted]
6	1 week treatment phone call	[redacted]
7	2 weeks treatment in-person visit	[redacted]
8	3 weeks treatment phone call	[redacted]
9	4 weeks treatment phone call	[redacted]
10	5 weeks treatment phone call	[redacted]
11	6 weeks treatment in-person visit (End of Treatment)	[redacted]
12	2 months post TKA phone call	[redacted]
13	3 months post TKA in-person visit	[redacted]

6.7 Study Duration

The duration of this study is expected to be approximately 2 years. We anticipate enrolling 2 subjects per month. Each subject's participation will last approximately 4 months.

6.8 Early Termination

It is possible that this study may be terminated prior to enrolling 36 subjects. As a result of the study design, the results will be reviewed and evaluated throughout the study as each subject completes his/her participation. If the results are less favorable than anticipated the study may be terminated early. Similarly, if it is found that the study yields results that are more favorable than expected, the study may be terminated earlier than expected. Any decision to terminate the study will be promptly reported to the IRBs and FDA.

6.9 Subject Compensation

Subjects will [redacted] compensation for taking part in all study visits. Compensation will be based on the subject completing milestones within the study. The disbursement schedule will be as follows:

- [redacted]0 after the completion of Visit 1 – Consenting
- [redacted] after the completion of Visit 2 – Lead Placement and Testing
- [redacted] after the completion of each Visit 4, 5 (only one instance), 7, 11, and 13
- [redacted] after the completion of each Visit 6, 8, 9, 10, and 12

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

In addition to payment for study participation, transportation can be arranged for subjects or mileage compensation can be provided at the current federal mileage rate for travel to visits. [redacted]

7.0 DATA MANAGEMENT

7.1 Subject Screening and Identification Log

A subject screening log will be completed at the investigational site for all subjects who were considered for the study. Those individuals who are excluded will be listed along with the reason for exclusion. Any subject who signs an Informed Consent and does not proceed with procedures associated with lead placement or fails to meet eligibility (*e.g.*, positive pregnancy test) will be considered a screen failure. The Informed Consent form will be filed in the screening binder.
The Subject identification log will be completed for subjects enrolled in the study.

7.2 Data Collection

Case Report Forms (CRFs) will be completed for each subject who signs an informed consent form up until the point of discharge from the study. CRFs will be completed and maintained in a fashion that is consistent with accepted Good Clinical Practices. CRFs will be completed in permanent blue or black ink and all entries will be made in a legible fashion. All fields will be completed. If necessary, corrections 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 CRFs and questionnaires.

All CRFs will be stored in a locked storage facility (either a locked office or a locked cabinet).

7.3 Subject Numbering

Eligible (*i.e.,* meeting all selection criteria through Visit 2) consecutive subjects will be given a unique alpha - numerical Subject ID number. Two-digit numbers will be assigned consecutively to each subject starting at 01. The letter will designate the site. A master list linking the subjects to the unique Subject ID numbers will be kept by the study staff in a secure location.

7.4 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. Subjects will be informed that the sponsor, the IRB, and regulatory authorities will have access to records that identify them as individuals. All applicable HIPAA regulations will be followed.

7.5 Data Processing

SPR Therapeutics, LLC will be responsible for database creation, data entry, generation of database queries, and data analysis.

All CRFs will be monitored by SPR Therapeutics personnel (or their authorized representatives). Completed, monitored forms will be returned to SPR Therapeutics for entry into the database. Visual checks will be completed for generation of site queries. The Investigational Site will be queried for missing data, inconsistent data, or illegible information via Query Forms. Following site query resolution, all Query Forms will be returned to SPR Therapeutics for inclusion into and/or modification of the study database.

8.0 DATA ANALYSIS

All primary and secondary outcome data will be analyzed and reported. Each site or individual surgeon may be analyzed separately. This study is a case series involving up to 36 subjects. The purpose of this study is to determine the treatment effect of PNS therapy for the treatment of knee pain following TKA. The outcomes of this study will also provide preliminary data to support and refine subsequent studies of this therapy for postoperative knee pain following TKA.

8.1 Analysis of Outcomes and Exploratory Measures

A table of outcomes and exploratory measures to be collected during the study can be found in Appendix A.

Question 5 of the Brief Pain Inventory-Short Form (BPI-5) is an 11-point numerical rating scale rating "Average Pain". The BPI-5 will be measured at Visit 1 to establish a baseline score, as well as daily during stimulation and monthly post-EOT. For each subject, the mean over the first 4 weeks following TKA surgery will be calculated. An overall mean across all subjects for the first 4 weeks following TKA surgery will be calculated as well. This outcome will also be compared to historical controls (e.g., published data).

Additionally, sub-analyses will be performed to determine the mean over different post-operative phases (such as acute (e.g., days 1-7) or subacute (e.g., days 7-28)); calculate the mean for each subject and across subjects up to End of Treatment (week 6); and evaluate the proportion of subjects with pain below a certain threshold (e.g., 4/10).

Subjects will also rank their daily "Average Pain" (BPI-5) while walking. These data will undergo the same analysis as listed above for the standard BPI-5. This outcome will also be compared to historical controls (e.g., published data).

At the weekly visits during stimulation, subjects will be asked to report their weekly "Average Pain" (BPI-5) while at rest. The mean over different intervals (such as weeks 1-4 or weeks 1-6) will be calculated.

At each study visit, pain treatments and analgesic usage will be recorded. Changes in analgesic usage will be calculated using morphine equivalent dosing (MED). The usage of analgesics over various intervals (such as weekly averages, during weeks 1-4, etc.) will be calculated. Medication usage will also be compared to pain scores to examine the correlation between analgesic usage and pain. The time to cessation of opioid will be determined. Also at each study visit, subjects will be queried for opioid related side effects. The number of effects noted over various intervals will be calculated.

Range of motion [redacted] will be collected at visits before, during, and after treatment. The time to achieve milestones (e.g., 90 degrees flexion, 100 degrees flexion) will be calculated for each subject and across all subjects. The mean flexion, extension, and range of motion (flexion – extension) across all subjects will be determined. The same will be calculated for passive ROM and active ROM.

Functional tests performed during the study will include the Timed Up and Go (TUG) test, the Six-Minute Walk Test, and the Fixed Distance Walk Test. The TUG test will be analyzed to determine the mean time across subjects at each time point. The 6MWT will be used to calculate the mean distance across subjects at each time point. Data from the Fixed Distance Walk Test will be used to compute the mean time across subjects at each time point.

Surveys performed during the study will include the Western Ontario and McMaster Universities Arthritis Index (WOMAC), Pain Interference (as measured by question #9 of the Brief Pain Inventory), Patient Global Impression of Change (PGIC), time to meet recovery milestones, Subject Satisfaction Survey, and Clinician Satisfaction Survey. The WOMAC will be used to calculate a mean total score across all subjects, means score of specific subsections or individual questions, and to calculate differences in scores post-operatively compared to pre-operatively. BPI-9 will be used to calculate differences in scores post-operatively compared to pre-operatively for individual subjects as well as across all subjects. A mean PGIC score will be calculated across all subjects. The time to meet recovery milestones will be used to compute the mean number of days to achieve each milestone. Frequency of answers will be determined for specific questions of the Subject Satisfaction Survey and Clinician Satisfaction Survey.

Throughout the study, subjects will complete self-shaded diagrams of areas of pain [redacted] The mean and standard deviation of the percent overlap will be calculated across subjects.

8.2 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.

A potential source of data loss is the failure of the subjects to return their completed diaries. Thus, subjects may receive reminder calls from the clinical study staff before certain visits to remind them to bring their completed diaries with them to the visit.

Subject withdrawal from the study is a potential source of data loss. Study investigators and staff will be trained to have clear discussions with subjects considering withdrawing from the study. [redacted]

Subjects are offered compensation for each visit as it is completed, including unscheduled visits, even if they do not complete all the visits. This compensation is intended to cover costs associated with taking the time to participate in the study. Sites are also provided with a travel budget for which they are able to reimburse subjects for the actual incurred mileage or mobility transportation arrangements can be provided.

If a subject is unable to return any follow-up diary, the data will be replaced using the one-week recall data (question #5 of the validated BPI-SF). The question may be collected verbally over the phone if needed. This method will mitigate the problem of missing data and minimize the need to impute scores. Scores will only be imputed if recall data are unavailable and cannot be obtained. If the subject later returns the diary, the diary data will be used over the one-week recall data.

Additional steps will be taken as necessary to maintain a high level of subject participation and follow up. For example, if a subject relocates during the study, arrangements will be made either to provide transportation for the subject to attend their visits at the clinical site, or to allow the subject to receive the necessary follow up at a medical center in closer proximity to their new location and a referring physician located near the subject will conduct the visit with the assistance of an investigator and/or a technical representative from SPR Therapeutics as needed.

8.3 Safety Endpoint Analysis

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

9.0 STUDY MONITORING

9.1 Training

SPR Therapeutics or their designee 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, Case Report Forms (CRFs), study specific procedures, Investigator Responsibilities, and Good Clinical Practices (GCPs) among the clinical research monitors and the Investigational Site team.

9.2 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]

[redacted]

9.3 Device Accountability

Device accountability will be maintained by the Investigational Site. [redacted]

9.3.1 Returning used devices to SPR Therapeutics

The site will record any devices returned to SPR Therapeutics in the Device Accountability Log. The site will contact SPR to obtain a Return Goods Authorization (RGA) number prior to returning any devices.

9.4 Designation of Study Monitor

SPR Therapeutics or a designated qualified study monitor will monitor this study.

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

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

10.0 ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

Adverse events (AEs) that occur during the study will be captured on 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). Adverse events will also be classified as serious or non-serious. 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. Side effects from narcotic therapy will be collected but not reported as adverse events.

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.

[redacted]

Table 2 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]			

It is the responsibility of the investigator to inform his/her 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.

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.

If the treatment is successful, subjects may experience some or all of the following benefits during and/or after stimulation:

- A reduction in the degree of pain (pain intensity).
- Increased tolerance of rehabilitation exercises, potentially decreasing the duration of in-hospital recovery and accelerating return to normal function
- Decreased probability of chronic postoperative pain resulting from unresolved acute postoperative pain

This research may benefit future patients with postoperative pain following TKA.

11.2 Known and Anticipated Risks

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

1) Risks associated with insertion of the needle introducer for lead placement

[redacted]

2) Risk of nerve damage from the needle or lead.

[redacted]

[redacted]

3) Risk of skin irritation, infection, or inflammation at the lead exit site

[redacted]

4) Risk of the percutaneous lead breaking beneath the skin

[redacted]

[redacted]

[redacted]

5) Risks associated with retained Percutaneous Lead fragments

[redacted]

[redacted]

6) Risks associated with lead fragment removal

[redacted]

7) Risk of lead replacement

[redacted]

8) Risk of skin irritation under the Sprint pad, Smartpatch lead connector tape, bandages, or belt

[redacted]

9) Risk of mechanical or electrical failure of the Sprint stimulator

[redacted]

10) Risks for pregnant women

[redacted]

11) Risk of discomfort or increased pain

[redacted]

12) Risk of worsening of pain symptoms

[redacted]

13) Risk of tissue damage

[redacted]

14) Risk of falls

[redacted]

15) Risks associated with Diathermy

[redacted]

[redacted]

16) Risks associated with MRI

[redacted]

[redacted]

17) Risk of allergic reaction to local anesthetics (if applicable)

[redacted]

18) Risk associated with venipuncture (if applicable)

[redacted]

19) Risk associated with conscious sedation (if applicable)

[redacted]

20) Risk of loss of confidentiality

[redacted]

21) Risk of swallowing or choking on battery

[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. 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. Though subjects may experience no benefit to participating in this study, the knowledge gained from the results and the application of that knowledge toward the future development of a stimulation system may benefit future patients and significantly improve the quality of life for patients suffering from postoperative pain following TKA. The potential risks of participation in this study have been minimized such that they are unlikely to occur and/or have non-serious consequences. The knowledge gained from the study and the potential for temporary relief of pain justifies the minimal potential risk.

11.4 Risk Justification

The proposed study presents a justifiable risk to the subjects based on the following rationale:

[redacted]

[redacted]

12.0 ETHICAL CONSIDERATIONS

12.1 Declaration of Helsinki

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.

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.

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.

12.3 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.

12.4 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.

13.0 STUDY ADMINISTRATION

13.1 Record Retention

By signing the Investigator Agreement, 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.

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. Principal Investigators, IRBs, and the FDA will be notified in writing in the event of a study termination.

Possible reasons for study termination include, but are not limited to the following: 1) the discovery of an unexpected, significant, or unacceptable risk to the participants enrolled in the study or 2) a decision on the part of SPR Therapeutics to discontinue or suspend the development of the device.

13.3 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]

13.4 Investigator Qualifications/Responsibilities and Investigator 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]

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Appendix A: Schedule of Subject Visits

		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5a, b, c...	Visits 6, 8, 9, 10	Visit 7	Visit 11	Visit 12	Visit 13
		Consent / Baseline	Place Leads	Follow-up Phone Call[+]	Day of TKA	In-hospital visits prior to discharge	Weekly phone calls	2 Week Post TKA Visit	6 Week Post TKA Visit / EOT	2 months after TKA Phone Call	3 months after TKA
Study Procedures	Informed Consent	X									
	Inclusion/ Exclusion	X	X								
	INR collected		X								
	Pregnancy Test		X								
	Inspect bandages and Lead exit site				X	X		X	X		X
	Lead Placement		X								
	Start Stimulation		X*		X						
	Remove Lead								X		
	Assess AEs		X[+]	X	X	X	X	X	X	X	X
Pain	Daily diary		X		X	X	X	X	X		
	BPI-5 [redacted]	X					X	X	X	X	X
Characterizing Stimulation	Patient-shaded leg diagram of pain		X		X	X*		X*	X		X*
	[redacted]		X		X	X	X	X	X		
	stimulation intensities		X		X			X	X		

Function	ROM & pain during ROM		X			X		X	X		X
	Fixed distance walk test□	X				X°					
	6 Minute Walk Test□	X						X	X		X
	TUG Test□	X				X°		X	X		X
Surveys	WOMAC	X				X°		X	X		X
	PGIC					X°	X	X	X	X	X
	BPI-9	X				X	X	X	X	X	X
	Subject Satisfaction Survey								X		
	PCS	X							X		X
	Time to recovery milestones					X	X	X	X	X	X
Medications and side effects	Record pain treatments/ Analgesic usage	X	X		X	X	X	X	X	X	X
	Opioid-related side effects	X	X			X	X	X	X	X	X

* Optional

o [redacted]

\+ [redacted]

□ Functional outcomes (Fixed Distance Walk Test, 6 Minute Walk Test, TUG Test) will only be administered if deemed safe by the clinical or physical therapy staff. Functional outcomes at the in-hospital visits after TKA surgery (Visit 5) must be assessed by the physical therapy staff; functional outcomes after these visits can be assessed by either study staff or physical therapy staff at the investigator's discretion.