EFFECT OF POSTOPERATIVE PERCUTANEOUS PERIPHERAL NERVE STIMULATION ON ACUTE AND CHRONIC AMPUTATION PAIN

Hunter Holmes McGuire VA Medical Center
Richmond, VA

Denise Lester, M.D., Brooke Trainer, M.D., Robert Trainer, D.O.
Douglas Murphy, M.D., Michael Amendola, M.D., Erik Baker, D.O.
Thomas Phan, M.D., Claudia Kem-Bumbala, R.N.
Christina Johnson, P.A., Kenneth Stutz, P.A.

Protocol version 1.2 – June 11, 2018

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1.0 Purpose and Objectives

1.1 Purpose

This prospective randomized controlled trial evaluates the feasibility of using percutaneous peripheral nerve stimulation (PNS) to reduce acute post-surgical pain in nontraumatic lower extremity amputation and decrease the incidence and/or severity of chronic phantom limb pain (PLP) or residual limb pain (RLP). The use of a novel, intentionally reversible, single-lead, PNS system has demonstrated promising results in the management of chronic pain syndromes including PLP and RLP (7). This study will apply the same PNS system to nontraumatic transfemoral or transtibial amputees (TFA or TTA, respectively) in the post-operative setting within 5-7 days after surgery to evaluate the feasibility and efficacy of peripheral nerve stimulation in the management of acute and chronic PLP and RLP.

1.2 Objectives

The goal of this study is to demonstrate that PNS is a safe, effective method of reducing acute and chronic pain in the nontraumatic lower extremity amputee, and can lessen the use of opioid pain medications. This pilot study will evaluate the feasibility of recruitment, randomization, retention, assessment procedures, and implementation of PNS in the acute post-operative period to develop a larger, multicenter, blinded, placebo-controlled, randomized clinical trial to evaluate efficacy in reducing acute and chronic PLP and RLP. Upon completion, we will assess the reliability and validity of the proposed study design. In conducting this investigation, we hope to answer the following questions:

- What is the feasibility of placing a PNS system in a transfemoral or transtibial amputee in the acute post-operative period?
- Does PNS produce clinically significant reductions in acute PLP or RLP?
- Does the application of PNS in the acute post-operative period reduce the incidence and severity of chronic PLP and RLP?
- Can PNS lessen the use of opioid and non-opioid pain medications?
- Does PNS affect time to prosthesis fitting, function outcomes (Functional Independence Measure [FIM] scores), wound healing, incidence of neuromas, time to hospital discharge, 30-day readmission rate, and hospital discharge survey answers?

1.3 Study Hypothesis

Percutaneous peripheral nerve stimulation may provide clinically significant relief of acute post-surgical pain in nontraumatic lower extremity amputation and decreases the incidence and/or severity of chronic PLP and RLP when applied in the acute post-operative setting.

2.0 Background and Significance

2.1 Background

Amputees commonly experience acute and chronic post-amputation pain. Amputation leads to persistent pain in up to 70-90% of patients, resulting in decreased quality of life, increased risk of depression, and negative impacts on interpersonal relationships and ability to work (10). The prevalence of persistent PLP or RLP in amputees is estimated to range from 45 to 74% for RLP and 51 to 85% for PLP (11, 12). Pain secondary to loss of limb, rather than the loss of limb itself, has a larger effect on ability to perform activities of daily living, complete simple tasks, and shows a negative correlation with return to work (13). Post-amputation pain can also impact the ability to use a prosthesis.

When present, post-amputation pain is difficult to manage. More than 50 different treatments have been developed for PLP, yet most have been unsuccessful (1). In many studies, acute PLP intensity was the only

significant independent predictor of chronic PLP intensity at 6 and 12 months after amputation (2). Liu et al have demonstrated the most significant risk factor for post-procedure pain (PPP) for total knee and total hip arthroplasties to be acute postoperative pain (3). Increased postoperative Visual Analog Scale (VAS) scores on days 1 to 5 has correlated with PPP at 3 months (4).

Perioperative pain management in lower extremity amputations commonly involves a multimodal approach utilizing pharmacologic and interventional therapies (8). Both acute and persistent post-amputation pain is commonly managed with opioids which are associated with undesirable adverse effects such as nausea, vomiting, sedation, and respiratory depression. Further, they often result in unsatisfactory reductions in post-amputation pain and have the potential for addiction and misuse (14). Several interventional therapies are available for use in the perioperative setting, however there is no consistent therapy that has been shown to prevent the development of persistent post-amputation RLP or PLP (8). Karanikolas et al demonstrated that optimized epidural analgesia and/or intravenous patient-controlled analgesia (PCA) in the perioperative setting decreases PLP intensity, prevalence, and frequency at 6 months after amputation (23). This study did not assess sustained pain relief beyond 6 months, and RLP was not significant in the study population.

Peripheral nerve catheter based pre-emptive analgesia has become an essential component of Standard Medical Therapy (SMT) at the Hunter Holmes McGuire VA Medical Center (VA) in lower extremity amputations to prevent onset of chronic pain, decrease opioid use, and decrease health care utilization (both inpatient and outpatient). The efficacy of peripheral nerve catheter-based regional analgesia for pain relief in the immediate postoperative period is well documented. However, associated motor, sensory, and proprioceptive deficits can increase the risk of falling (15) and duration of use is limited due to risk of infection (16). This intervention is limited by the fact that peripheral infusion catheters (typically femoral and sciatic nerve catheters) must be removed by postoperative day 5 to reduce the risk of infection. Furthermore, Apfelbaum demonstrated in a large study that many patient's worst incidence of postoperative pain occurs after discharge (5). Given this safety limitation and the need for continued pain control in the entire perioperative period, this study seeks to augment this therapy with a percutaneously placed PNS system. This is expected to extend the period of perioperative pain control to greater than 30 days and beyond. There is convincing evidence in studies thus far showing that when a PNS system is applied to chronic pain sufferers, it can extend the treatment effect well beyond the time in which it is implanted. To date, the system studied is the only intentionally reversible, percutaneously placed PNS system. More comprehensive and earlier treatment of acute pain is believed by many in the field to be even more effective (6,7).

2.2 Literature Review

PNS has been studied for the treatment of some chronic pain syndromes (7, 17-19), including persistent post-amputation pain. The mechanism of action of peripheral nerve stimulation in pain relief is commonly explained using the "gate control theory" of Melzack and Wall (20). This theory explains that electrical current-induced activation of large-diameter myelinated afferent peripheral nerve fibers inhibits the transmission of pain signals from small-diameter pain fibers to the central nervous system at the level of the spinal cord (15). Rauck et al (7) showed that 9 of 14 subjects who completed two-weeks of PNS therapy reported reductions in mean daily worst post-amputation pain, average RLP and PLP, and interference from RLP and PLP at least one month after the end of treatment. Interference from RLP or PLP refers to how pain has interfered with general activity, mood, walking ability, work, relations with others, sleep, and enjoyment of life. PNS was shown to be effective in reducing post-amputation pain when most pain is confined to one or two nerve distributions (7, 21-22). Results showed that 14 of 16 subjects reported ≥75% paresthesia coverage from PNS, obtained clinically significant pain relief, and proceeded to a 2-week home trial with this system. 9 subjects completed the 2-week trial and 5 subjects did not complete the trial because

of accidental dislodgement (N=2), temporary discomfort near the lead (N=2), and return of post-amputation pain despite stimulation (N=1). The 9 responders who completed the home trial reported reductions in their mean daily worst post-amputation pain (56 ± 26%, 56 ± 26%, N = 9), average residual limb pain (72 ± 28%, 42 ± 27%, N = 7), average phantom limb pain (81 ± 28%, 47 ± 48%, N = 7), interference from residual limb pain (81 ± 27%, 53 ± 17%, N = 6), interference from phantom limb pain (83 ± 31%, 56 ± 46%, N = 7), and Pain Disability Index (PDI) (70 ± 38%, 55 ± 32%, N = 9) during the 2nd week of stimulation and 4 weeks after the end of stimulation, respectively. All 9 responders rated their change in quality of life as improved at the end of stimulation and at the end of the 4-week follow-up period.

3.0 Scientific Rationale and Study Design

3.1 Scientific Rationale

The feasibility of using PNS to reduce acute postoperative pain is not currently well documented in medical literature. A preliminary report demonstrated the use of PNS to treat pain after total knee arthroplasty in 10 subjects who experienced postoperative knee pain difficult to control with oral analgesics between 6 and 97 days after surgery. Nine out of 10 subjects experienced at least 57% decrease in pain, and half had complete resolution of pain at rest (9). The application of PNS in the treatment of acute postoperative amputation pain and the efficacy of using PNS to prevent or reduce the severity of persistent PLP or RLP has not been documented.

Currently, literature documenting the use of PNS in postoperative amputation pain is limited. The PNS system in this study has been used previously to evaluate the reduction in chronic post RLP or PLP (7). There is an ongoing multi-site investigation evaluating the use of PNS in chronic pain after traumatic lower extremity amputation. To date, there is no study that documents the use of PNS therapy in the acute postoperative period after TFA or TTA. This study aims to report on the feasibility and efficacy of using PNS in this clinical setting to evaluate reductions in acute post-amputation pain, incidence or severity of chronic post-amputation pain, and reliance on opioid medications amongst other outcome measures as described in *Section 4.0: Study Outcomes and Exploratory Measures*.

3.2 Study Design

This prospective randomized controlled trial aims to assess the feasibility of using a novel percutaneous peripheral nerve stimulator system to produce clinically significant reductions in acute post-surgical pain after nontraumatic lower extremity amputation, and evaluate reductions in the incidence and/or severity of chronic PLP or RLP. Subjects who have moderate pain 2 to 7 days after transfemoral or transtibial amputation surgery will be enrolled and randomized to Group 1 ("Treatment Group") or Group 2 ("Control Group"). Subjects in Group 1 will be treated with 30 to 60 days of PNS in addition to SMT. Subjects in Group 2 will be treated with the SMT alone. SMT is defined as the same routine medical care given to all patients, regardless of whether they are enrolled in the study. This may include, but is not limited to non-opioid and opioid pain medications, regional anesthesia peripheral nerve blockade, daily postoperative visits by the Acute Pain Service, and follow-up appointments in the Interventional Pain Clinic.

- Group 1: 30 to 60 days of peripheral nerve stimulation starting within 7 days after surgery and Standard Medical Therapy
- Group 2: Standard Medical Therapy only

Subjects are evaluated daily by study investigators from the time of study enrollment to hospital discharge. Subsequent telephone or outpatient clinic evaluations occur at intervals which are detailed in the *Schedule of Study Procedures* (Appendix**)**.

4.0 Study Outcomes and Exploratory Measures

4.1 Primary Outcomes

4.1.1 Effect of PNS on acute pain after lower extremity amputation

The Brief Pain Inventory Short Form (BPI) is a 9-item questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate their worst, least, average pain, and rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale. Levels of PLP and RLP are re-assessed at follow-up Visits according to the Schedule of Study Procedures. Questions used to assess pain or sensation are listed below. For BPI #3, #4, and #5, responses are recorded on an 11-point scale from "0" to "10" with "0" defined as "No Pain" and "10" defined as "Pain as Bad as You Can Imagine."

- Check yes or no if you experienced any (phantom limb or residual limb) sensation in the last 24 hours.
- BPI #3: "Please rate your (phantom limb or residual limb) pain by marking the box beside the number that best describes your pain at its **worst** over the last 24 hours."
- BPI #4: "Please rate your (phantom limb or residual limb) pain by marking the box beside the number that best describes your pain at its **least** over the last 24 hours."
- BPI #5: "Please rate your (phantom limb or residual limb) pain by marking the box beside the number that best describes your pain on the **average** over the last week."

4.1.2 Effect of PNS on the incidence and severity of chronic pain after lower extremity amputation

Chronic pain (i.e. pain persisting for more than 2 to 3 months after TFA or TTA surgery will be evaluated using BPI questions #3, #4, and #5 as above at follow-up Visits according to the Schedule of Study Procedures. Data will be compared between groups to assess for differences in the incidence and severity of chronic pain.

4.2 Secondary Outcomes

4.2.1 Interference due to Pain

BPI #9 will be assessed at intervals defined in the Schedule of Study Procedures. This question asks subjects to rate how pain has interfered with various aspects of life: "Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your: (a) General activity (b) Mood (c) Walking ability (d) Sleep (e) Enjoyment of life." Responses are recorded on an 11-point scale from "0" to "10" with "0" defined as "Does Not Interfere" and "10" defined as "Completely Interferes."

4.2.2 Patient Global Impression of Change (PGIC) Scale

Participant ratings of global improvement are one of the core outcome domains in chronic pain studies (Dworkin et al. 2005). Patient Global Impression of Change (PGIC) Scale is assessed at intervals defined in the Schedule of Study Procedures, which rates perception of change in activity limitations, symptoms, emotions, and overall quality of life in relation to pain since beginning treatment. The scale ranges from 0 defined as "No change" to 7 defined as "A great deal better, and a considerable improvement that has made all the difference." Responses are collected by telephone or outpatient office evaluations in the Interventional Pain Clinic.

4.2.3 Pain Disability Index (PDI)

The Pain Disability Index (PDI) a simple and rapid instrument for measuring the impact that pain has on the ability of a person to participate in essential life activities. This can be used to evaluate patients initially to monitor them over time and to judge the effectiveness of interventions. The index was developed at St. Louis University Medical Center. PDI) is assessed at intervals defined in the Schedule of Study Procedures, which measures subjects' disruption in various aspects of life secondary to **chronic pain**, including family/home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activities. Each category is rated on an 11-point scale from "0" to "10" with "0" defined as "No Disability" and "10" defined as "Worst Disability." Responses are collected by telephone or outpatient office evaluations in the Interventional Pain Clinic.

4.2.4 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).

4.2.5 Analgesic use and Opioid-related Side Effects

All opioid and nonopioid pain medication use will be assessed at intervals according to the Schedule of Study Procedures. The Virginia Prescription Monitoring Program Database will be queried. Subjects will be asked if they are taking any medications for pain. Subjects will be asked to count their remaining number of pills of narcotic pain medication at each follow-up encounter.

4.2.6 Functional Independence Measure (FIM)

The FIM provides a uniform system of measurement for disability based on the International Classification of Impairment, Disabilities and Handicaps. The FIM instrument measures the level of a patient's disability and indicates how much assistance is required for the individual to carry out activities of daily living. A baseline mobility FIM will be recorded with the assistance of the Department of Physical Therapy shortly after amputation but before stimulator placement (Group A) and follow-up FIM will be recorded at the 4 and 8-week outpatient clinic visits. Improvement in FIM will be evaluated and compared between groups.

4.2.7 Patient Outcomes and Hospital Discharge Survey

Other secondary outcomes including time to prosthesis fitting, wound healing, incidence of neuromas, time to hospital discharge 30-day readmission rate, and hospital discharge survey will be documented from the electronic medical record and compared between groups.

5.0 Study Protocol

5.1 Study Materials

The SPRINT™ Peripheral Nerve Stimulator (PNS) System will be used by subjects in Group 1. Up to two SPRINT Systems (i.e. 1 lead per stimulator) will be used by each subject.

5.2 Concurrent Medications and Non-Drug Therapies

Subjects in both groups will receive SMT, which may include medication and/or non-drug therapies. However, subjects in both groups should not perform any rehabilitation activities that may conflict with the device Instructions for Use (such as water therapy) during the study.

5.3 Patient Recruitment

Patients planned for nontraumatic TFA or TTA will be screened at the Vascular Clinic. A Waiver of Informed Consent for Recruitment Purposes and a Waiver of Authorization for Recruitment Purposes will be submitted to the Institutional Review Board (IRB). Protected Health Information (PHI) will be used to locate and review appropriate medical records (CPRS, and paper medical records) to determine study eligibility. If a patient appears to meet all eligibility criteria (see Eligibility, Section 5.4), then he/she will be contacted by study investigators and given information detailing study objectives, procedures, follow-up encounters, assessments, and potential risks and benefits. If the patient agrees to participate, he/she will be asked to sign the Consent Form. Study staff will explain the process randomization, lead placement, data collection, and follow-up encounters. All baseline information and outcome measurements will be collected and recorded on the appropriate Case Report Forms.

5.4 Eligibility

5.4.1 Inclusion Criteria

Inclusion criteria are nontraumatic transfemoral or transtibial amputation (TFA or TTA, respectively) and age over 18..

5.4.2 Exclusion Criteria

Exclusion criteria are systemic infection, immunosuppressive disorder, implanted electronic devices, pregnancy, previous allergy to skin contact materials and/or anesthetic agent altered mental status, inability to provide consent, greater than 180 morphine equivalents (MED) per day.

5.5 Study Plan

The study includes 13 Visits. Please refer to the Appendix for a schedule of study procedures for both groups as well as outcomes measured at each visit.

Patients planned for nontraumatic TFA or TTA will be screened by the study investigators who are working on the Acute Pain Service (APS). APS is usually consulted for all transfemoral and transtibial amputations to provide perioperative anesthesia, which typically includes placement of a peripheral nerve catheter for local anesthetic blockade. When a potential subject is identified, study investigators will begin a chart review for screening purposes. The investigators will review the medical record of potential subjects and complete Form 00 (Screening and Demographic Information). Chart review will include the collection of name, social security number and date of birth from CPRS, the ORC, and the Vascular Clinic. Protected Health Information (PHI) will be used to locate and review appropriate medical records (CPRS and paper medical records) to determine study eligibility. If a subject appears to meet all eligibility criteria (see Section 5.4. Eligibility), then he/she will be contacted by study investigators and given recruitment materials detailing study objectives, randomization, procedures, follow-up encounters, assessments, and potential risks and benefits. The subject will be provided with patient information pertaining to the peripheral nerve stimulator system under investigation. If permitted by the subject, a sponsor representative or their designee may be present at any of the study visits to advise on material handling and answer questions as needed.

Patients who are interested in participation will be asked to complete a Beck Depression Inventory (see Form BDI) to be screened for depression (must score 20 or less) prior to enrollment. Veteran participants who are evaluated by study staff and suspected to be depressed will be further evaluated by a psychiatrist or psychologist utilizing the Mental Health Consultation and Liaison Service at McGuire VAMC. Research study staff will page the C&L service at 351-1067 (Use *601 pager# 9198 after 4pm and on weekends) and then walk the participant to the C&L provider to facilitate the evaluation on the day that the participant

presents as depressed. If non-veterans participants are enrolled, arrangements made for him/her to be evaluated at a non-VA facility.

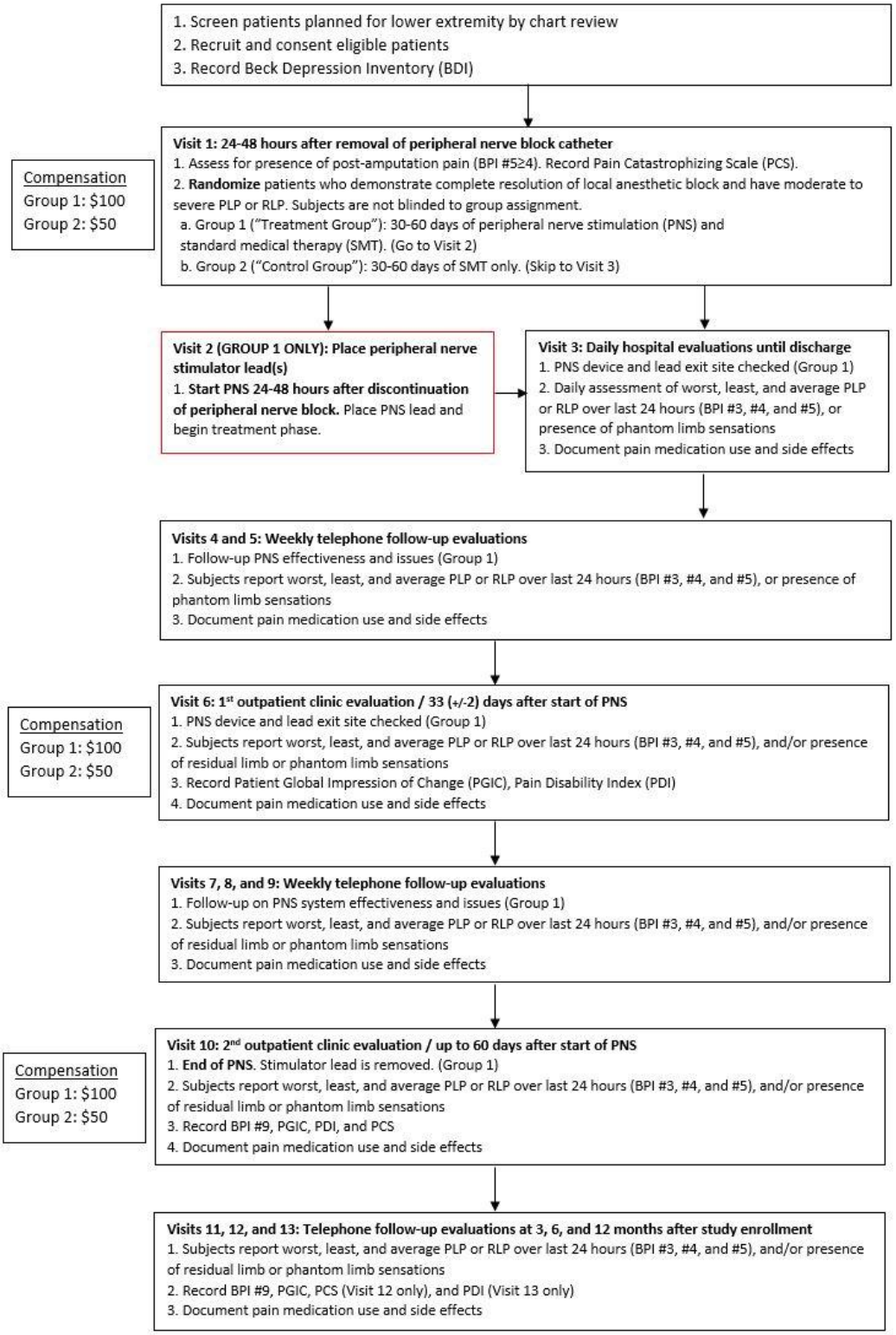

Figure 1 Subject flowchart.

Patients who agree to participate in the study will be asked to sign the Consent Form. Ideally, patients should provide informed consent and be enrolled in the study prior to surgery. Typically, the local anesthetic peripheral nerve block catheters (or single shock femoral or sciatic nerve blockade) are placed on the day prior to surgery or day of surgery. Subjects will be given the opportunity to enroll in the study when the catheter is placed, however, those who wish to decide on enrollment after their surgery may be enrolled up until the time in which their peripheral nerve block catheter is removed, which is usually by post-op day 5. Upon enrollment, subjects will be evaluated by APS daily.

The Consent Form will be scanned into the electronic medical record. Consent for photographic and video recordings will be requested. If collected, photographs and videos are intended for potential use in publications, future grant applications, and educational purposes. Subjects will receive a copy of their consent forms if requested. HIPPA Forms will be signed. The Schedule of Study Procedures outlines the baseline information and outcome measures recorded at each "Visit" on Case Report Forms (CRFs). All completed paper documents will be securely stored in a locked box placed in a fixed, locked file cabinet in the Interventional Pain Clinic on 2C. Only authorized study personnel will have the keys to access study materials containing protected patient information. A note may be documented in the patient's electronic medical record to indicate participation in the study. Subjects will be randomized to Group 1 ("Treatment Group") or Group 2 ("Control Group") (see Section 6.2. Sampling and Randomization Procedures).

5.5.1 Visit 1: 24-48 hours after removal of peripheral nerve block catheter

Subjects will be assessed at least 24-48 hours after removal of the peripheral nerve catheter (or after the effects of a single shot femoral and/or sciatic nerve block have worn off). They will be evaluated for post-surgical complications, and for the presence of phantom limb sensation or pain and RLP. Average pain severity and anatomic distribution will be reported by answering BPI-SF #2 and #5.

Subjects in Group 1 will proceed to Visit 2 and undergo placement of the peripheral nerve stimulator lead(s) by post-op day 7, in addition to receiving SMT. Subjects in Group 2 will skip to Visit 3. They will be treated with SMT and followed up by study investigators daily until discharged. They will subsequently be followed up by telephone according to the Schedule of Study Procedures.

5.5.2 Visit 2A: Placement of percutaneous peripheral stimulator leads (Group 1 only)

Subjects randomized to Group 1 proceed to placement of the stimulator leads by post-op day 7 to begin peripheral nerve stimulation therapy with the SPRINT™ PNS System (Figure 2.1). The procedure for placement of the peripheral nerve stimulator lead (Figure 2.2) is similar to placement of a peripheral nerve catheter for local anesthetic blockade. The main difference is that instead of delivering medications, electrical stimulation is applied to the peripheral nerve over a wide range of parameters. Also, the stimulator lead does not need to be placed as close to the nerve as a local anesthetic peripheral nerve catheter. This study will evaluate the application of one or two leads per subject: one for the femoral nerve and/or one for the sciatic nerve. Lead placement is expected to take up to 2 hours.

Before placement of the lead, test stimulation with a needle electrode is performed to determine an appropriate location for stimulator wire lead placement, assess for nerve function, and to confirm that the subject's pain is responsive to stimulation. The relevant section of the leg will be cleansed and a test stimulation needle electrode will be percutaneously inserted within 0.5-3 cm of the femoral nerve under mandatory ultrasound-guidance. For comfort, local anesthesia may be administered at the insertion site. The needle electrode is connected to the battery-powered electrical stimulator device, which is used to deliver electrical stimulation to confirm electrode placement distance from the nerve trunk. If the patient feels subcutaneous sensations proximal to the test needle, which indicates stimulation of afferent nerve

fibers in the local region superficial to the electrode, then the needle is advanced slightly (0.2-0.5 cm) and test stimulation is delivered again. The process of advancing the needle electrode and adjusting stimulus intensity is repeated in small increments until comfortable paresthesia as are evoked in the distal regions of postoperative amputation pain without causing uncomfortable sensations or unwanted motor contractions. If this is not achieved, the needle electrode is withdrawn, and the test stimulation procedure is repeated until a satisfactory location is determined. Once a suitable entry site is determined, the fine-wire stimulator lead will be placed. Each subject in Group 1 may undergo placement of one to two leads in relation to the femoral and/or sciatic nerves. The techniques and procedures described below may be adapted as needed on a case-by-case basis.

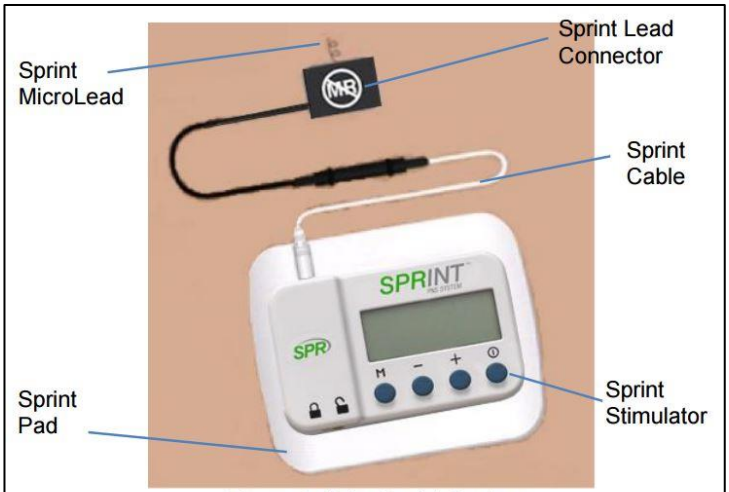

Figure 2.1 The Sprint System (key components)

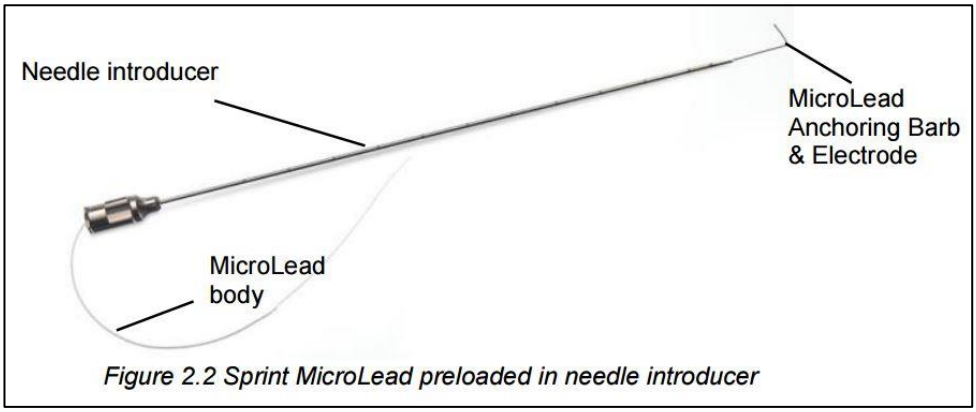

Figure 2.2 Sprint MicroLead preloaded in needle introducer

Lead placement near the femoral nerve uses an anterior approach guided by anatomic landmarks including the inguinal ligament, inguinal crease, and femoral artery. The subject will be in supine position with ipsilateral extremity slightly (approximately 10-20^{o}) abducted. The lead introducer is inserted near but below the inguinal crease and approximately 1 cm lateral to the pulse of the femoral artery.

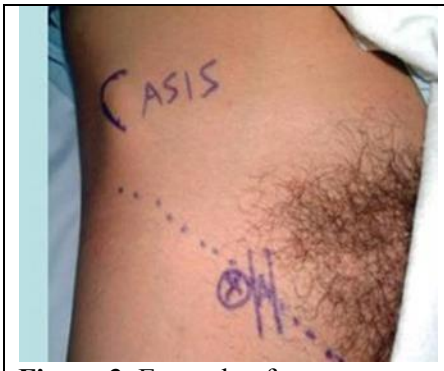

Figure 3. Example of a percutaneous anterior approach that may be used to access the femoral nerve. The inguinal crease (noted with dotted line), femoral artery (noted with an "A"), and needle insertion site (noted with a circled "X") are shown on the right leg.

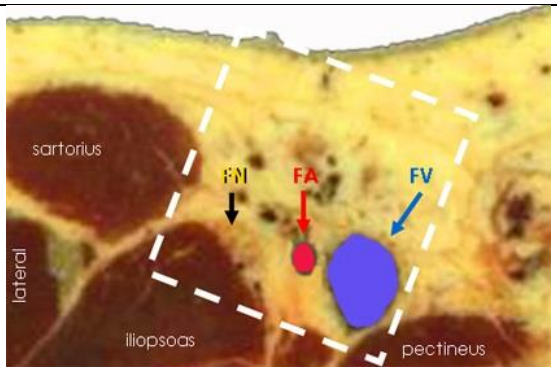

Figure 4. Cross section shows the femoral nerve (FN), femoral artery (FA), and femoral vein (FV) relative to surrounding structures of adipose tissue and muscle (e.g. sartorius muscle, iliopsoas muscle, and pectineus muscle; and the white dashed-line box indicates the area scanned in the ultrasound image in Figure 6.

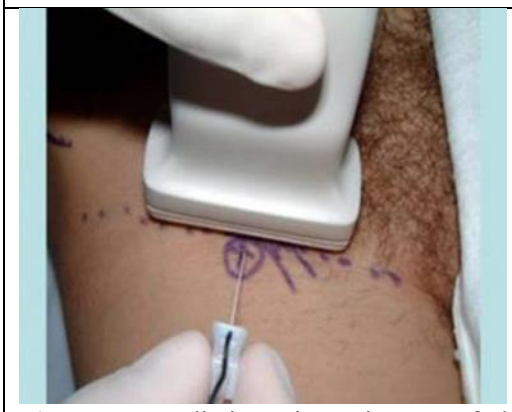

Figure 5. Needle insertion using out of plane ultrasound guidance (ultrasound transducer is perpendicular to the needle) is shown but in plane ultrasound guidance may also be used.

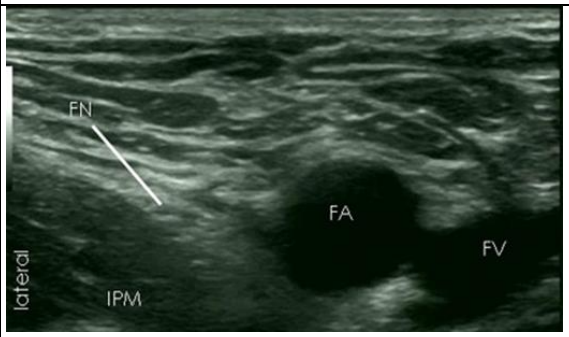

Figure 6. Ultrasound image shows the FN (at the bottom right tip of the white line) relative to the FA, FV, and the iliopsoas muscle (IPM) (adapted from Ultrasound for Regional Anesthesia).

Adapted from SPR Therapeutics™

Lead placement near the sciatic nerve uses the posterior transgluteal or subgluteal approaches that are commonly practiced in regional anesthesiology. Landmarks for the transgluteal approach include the greater trochanter and the posterior superior iliac spine. The subject is placed in lateral decubitus position, and the lead introducer is aimed approximately 4 cm distal to the midpoint between the greater trochanter and the posterior iliac spine to target the sciatic nerve. Landmarks for the subgluteal region include the

greater trochanter and the ischial tuberosity, and the lead introducer is aimed approximately 4 cm distal to the midpoint between the greater trochanter and the ischial tuberosity.

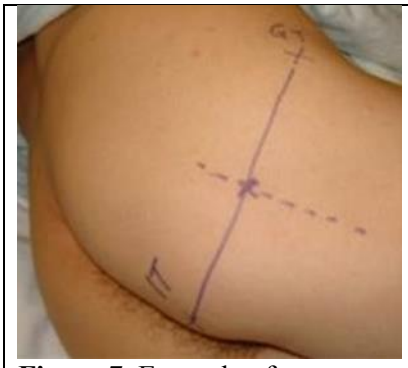

Figure 7. Example of a percutaneous posterior approach that may be used to access the sciatic nerve. The dashed line bisecting the line between the greater trochanter (GT) and ischial tuberosity (IT) indicates the sciatic nerve and the midpoint ("x") marks the needle insertion location

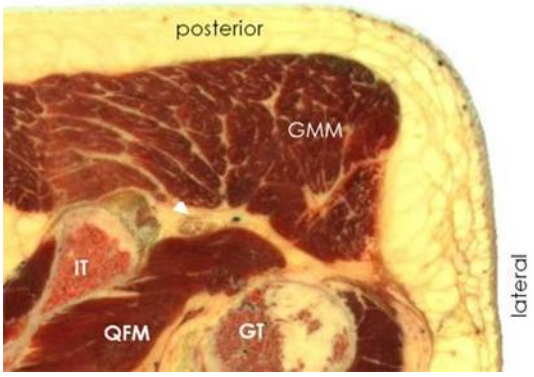

Figure 8. Cross section shows the sciatic nerve (arrowhead) surrounded by the gluteus maximus muscle (GMM), quadratus femoris muscle (QFM), adipose tissue, IT, and GT.

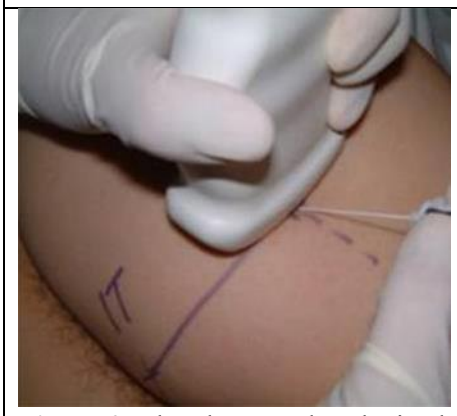

Figure 9. The ultrasound probe is placed perpendicular to the sciatic nerve to provide a transverse image as the needle is inserted.

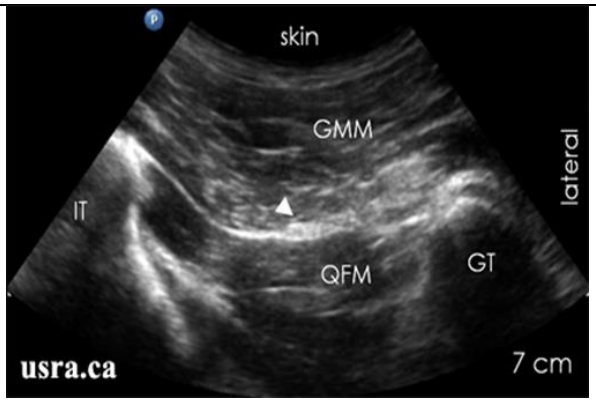

Figure 10. Ultrasound image shows the sciatic nerve (arrowhead) relative to surrounding structures (adapted from Ultrasound for Regional Anesthesia).

Adapted from SPR Therapeutics™

Alternate anatomic approaches for lead placement (e.g. popliteal approach for sciatic nerve) may be utilized to optimize safety and improve patient response. Once a lead has been placed, stimulus parameters will be adjusted to determine the settings necessary to evoke comfortable sensations that overlap with the regions of pain associated with TFA or TTA surgery. Parameters which can be adjusted include amplitude (mA), duration (μs), and frequency (Hz). Study staff will attempt to determine the parameters which produce the most comfort as endorsed by the subject. These parameters will vary from subject to subject and may be adjusted as needed throughout the study.

Once satisfactory lead placement and stimulus parameters have been achieved, subjects will begin the 30 to 60-day treatment phase. Subjects will be provided with a manual and educated on the use and care of the device. Stimulation may be delivered continuously up to 24 hours per day until the end of therapy.

Leads will be indwelling no more than a total of 60 days. If a lead is dislodged or broken prior to the end of therapy, the subject may be offered the opportunity for a lead replacement depending on their willingness to undergo the lead replacement procedure and time remaining in the treatment period.

If the subject provides media consent, photographs and video of the lead placement procedure may be recorded and are intended for potential use in publications, future grant applications, and educational purposes. Media may be stored on VA CAC access computers on a HIPAA-compliant share drive.

5.5.3 Visit 2B: Daily hospital evaluations until discharge

Subjects in both groups will be evaluated by study investigators daily until they are discharged. The length of stay is approximately 14 days for TFA per VASQIP 2016 quarter 4 data (Veterans Affairs Surgical Quality Improvement Program). Based on this data, subjects in Group 1 will likely be discharged 7 to 14 days after starting peripheral nerve stimulation. Group 1 subjects will be asked questions to re-assess the stimulation-evoked paresthesia coverage of the leg. Stimulator devices will be inspected to ensure appropriate function. Lead exit sites are inspected for skin irritation, infection, and inflammation. These risks will be minimized by using sterile leads and sterile technique. Maintenance, care of the leads and lead exit sites, and bandage changes will be performed as needed. Subjects in both groups will be evaluated for the presence of phantom sensations, as well as least, worst, and average PLP or RLP according to the Schedule of Study Procedures.

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5.5.4 Visits 3, 4 and 5: Weekly telephone follow-up evaluations

Visits 3, 4 and 5 consist of weekly telephone evaluations at 1, 2 and 3 weeks after starting peripheral nerve stimulation (Group 1) or discontinuation of peripheral nerve block (Group 2). If issues related to the peripheral nerve stimulator device or leads occur and cannot be resolved by telephone, subjects may be evaluated in the Interventional Pain Clinic as needed.

Subjects are asked to rate their worst, least, and average PLP and RLP (BPI #3, #4, and #5). A medical reconciliation will be completed during each phone evaluation by asking the subject how many pills of narcotic pain medications they have left and querying the Virginia Prescription Monitoring Program Database.

5.5.5 Visit 6: First outpatient clinic evaluation / 30 days after start of PNS

All subjects are asked to return to the Interventional Pain Clinic at 4 weeks after the start of peripheral nerve stimulation. Stimulator devices (Group 1) will be inspected to ensure appropriate function. Lead exit sites are inspected for skin irritation, infection, and inflammation. Maintenance, care of the leads and lead exit sites, and bandage changes will be performed as needed.

All subjects are asked to rate their worst, least, and average PLP and RLP (BPI #3, #4, and #5). Subjects will rate the degree with which pain has interfered with general activity, mood, walking ability, sleep, and enjoyment of life (BPI #9). Pain Disability Index (PDI) and Patient Global Impression of Change (PGIC) will be assessed. A medical reconciliation will be completed during each phone evaluation by asking the subject how many pills of narcotic pain medications they have left and querying the Virginia Prescription Monitoring Program Database.

5.5.6 Visit 7, 8, and 9: Weekly follow-up telephone evaluations

Visits 7, 8, and 9 consist of weekly telephone evaluations at 5, 6, 7 weeks after starting peripheral nerve stimulation (Group 1) or discontinuation of peripheral nerve block (Group 2). If issues related to the

peripheral nerve stimulator device or leads occur that cannot be resolved by telephone, subjects may be evaluated in the Interventional Pain Clinic if needed.

Subjects are asked to rate their worst, least, and average PLP and RLP (BPI #3, #4, and #5). A medical reconciliation will be completed during each phone evaluation by asking the subject how many pills of narcotic pain medications they have left and querying the Virginia Prescription Monitoring Program Database.

5.5.7 Visit 10: Second outpatient clinic evaluation / up to 60 days after start of PNS

All subjects are asked to return to the Interventional Pain Clinic at approximately 60 days after starting peripheral nerve stimulation (Group 1) or discontinuation of peripheral nerve block (Group 2). Stimulator leads will be removed by gentle traction. The lead will be visually inspected by study staff to evaluate for lead fracture In the case of a retained lead fragment, study staff will determine the most appropriate medical plan to further evaluate and treat the subject. In most instances, retained lead fragments do not need to be removed and are rarely associated with further complications. Lead exit sites are inspected for skin irritation, infection, and inflammation. Both groups will continue to be treated with SMT as needed until the end of participation in the study. Subjects in Group 1 are encouraged to complete the entire 60-days of peripheral nerve stimulation, however are free to discontinue treatment at any time during the treatment phase.

5.5.8 Visits 11, 12, and 13: Phone evaluations at 3, 6, and 12 months after study enrollment

Telephone evaluations for both groups occur at approximately 3, 6, and 12 months after study enrollment. Outcome measures to be assessed are listed in the Schedule of Study Procedures.

5.5.9 Unscheduled Visits/Lead Replacements

Unanticipated complications related to the PNS system may occur, including technical issues with the device, assistance with bandage change or lead exit site care, or adverse events requiring further evaluation by study staff. Most issues may be addressed by telephone. Subjects may return to clinic for further evaluation if necessary. Based on the discretion of the subject and study investigators, a decision may be made to allow the subject to continue in the study or be discharged.

5.6 Facilities and Resources

Subjects will be screened at the Vascular Clinic. Lead placement will take place in the Interventional Pain Clinic (IPC) or at the subject's bedside. Study data, recruitment materials, and sensitive patient information will be stored in a fixed, locked file cabinet in the IPC in 2C-117. Peripheral nerve stimulators and all related materials will be stored in a locked cabinet in the IPC. Devices will be labeled and designated specifically for research purposes. Only these labeled devices may be used in the study.

Study investigators who have received necessary training on the study procedures will be performing the placement of the peripheral nerve stimulator lead wire. Procedures include but are not limited to: (1) placement of stimulator lead under ultrasound guidance, (2) removal of stimulator lead at the end of the 30 to 60-day treatment period (3) replacement of stimulator lead (if applicable).

5.7 Study Staff

Denise Lester, M.D. (Principle Investigator (PI), Assistant Professor, Anesthesiologist and Algologist) oversees all research related activities and leads the research team in developing the experimental protocol, conducting data analysis, writing and editing literature for publication, placing the stimulators, and may assist with following up with subjects.

Douglas Murphy, M.D. (Project Mentor, Regional Amputee Center Medical Director, Polytrauma and Amputee Musculoskeletal/Ultrasound Fellowship Director) provides expertise in the care of amputees and assists with protocol development.

Brooke Trainer, M.D. (Co-Investigator, Assistant Professor, Staff Anesthesiologist, and Acute Pain Physician) will assist with development of the protocol, screening of subjects, data analysis, placement of the stimulators, and following up with subjects.

Robert Trainer, D.O. (Co-Investigator, Director of Interventional Pain Services, Anesthesiologist and Pain Physician) will participate in placement of the stimulators, follow up with subjects, and assist with protocol development and data analysis.

Erik Baker, D.O. (Co-Investigator, Staff Anesthesiologist, Acute Pain Physician) will participate in placement of the devices and follow up with subjects.

Michael Amendola, M.D. (Co-Investigator, Chief of Vascular Surgery) will assist with development of the protocol and follow-up with subjects in the Vascular Clinic.

Thomas Phan, M.D. (Co-Investigator, Physical Medicine and Rehabilitation PGY-3 resident) will assist with developing the research protocol, create the Case Report Forms and patient diary document, follow up with subjects, collect data, conducting data analysis, and write and edit literature for publication.

Claudia Kem-Bumbala, R.N. (Co-Investigator, Registered Nurse, Board certified by the American Nurses Credentialing Center for Pain Management) follow up with subjects and assist with clinical activities and procedures.

Christina Johnson, P.A. (Co-Investigator, Anesthesia Physician Assistant) will assist with screening and follow-up with subjects.

Kenneth Stutz, P.A. (Co-Investigator, Anesthesia Physician Assistant) will assist with screening and follow-up with subjects.

5.8 Study Duration

The duration of this investigation is expected to be 18-24 months. We anticipate enrolling 2-4 patients per month. Each patient's participation will last approximately 12 months.

6.0 Data Management

6.1 Sample Size

The investigation seeks to broaden the knowledge of the effects of neuromodulation on acute post-operative pain in nontraumatic lower extremity amputation. The aim is to evaluate the feasibility of implementing PNS in TFA or TTA in the acute post-operative period. 16 subjects will be randomized into two groups with 8 each**.** Sampling will not be restricted by race or gender. The sample size of 16 is expected to allow the investigators to conduct a cost-effective yet informative pilot study to assess the logistics of placing the device as described in this protocol, evaluate safety, and report any clinically significant differences in primary and secondary outcomes between Treatment and Control Groups. The study outcomes will be reported in nontraumatic TFA or TTA, many of which are secondary to dysvascular disease. Although this is a specific subset of all amputations that are performed, dysvascular disease accounts for a sizeable proportion of limb loss in the US with an estimated prevalence of 38-82% (24, 25). The results of this investigation will be used to refine the study design, recruitment, randomization, retention, and assessment procedures, and ultimately develop a larger, multicenter, randomized controlled trial to further evaluate

treatment efficacy, adverse effects, and cost efficiency. To improve generalizability, subsequent investigations will seek to include a wider subset of amputations which may be accomplished with the addition of more study sites.

6.2 Sampling and Randomization Procedures

Based upon historical data on amputations at the HHM-VAMC, there are estimated to be one to two amputations per week that would qualify for enrollment in this study. Subjects will be screened for enrollment through the vascular surgery clinic. A considerable proportion of vascular clinic patients will require lower extremity amputation and are usually scheduled for next day surgery due to the urgency of presentation. Study investigators will conduct a chart review of potential subjects and complete Form 01-A (screening and demographic information). Based on the chart review, if a patient appears to meet all eligibility criteria, then they will be contacted by study investigators for potential enrollment. If the patient agrees to participate, they will be consented and randomized to Group 1 or Group 2.

Prior to the start of this study, a member of the study staff that is not involved with recruitment or data evaluation will be responsible for generating a random string of group assignments long enough to fill all anticipated spots in this study. The numbers will be placed in secure envelopes by blocks of two. A block of two will contain one assignment to the Treatment Group and one assignment to the Control Group. As subjects are consented and enrolled in the study, they will be assigned an envelope which randomizes them to a group. Subjects are not blinded to their group assignments. Subjects in the Treatment Group will receive the investigational treatment (30 to 60-days of peripheral nerve stimulation) in addition to SMT. Subjects in the Control Group will be treated with the SMT alone.

6.3 Data Analysis

A table of outcome measures recorded during the study can be found in Appendix. Scores rating daily average, worst, and least pain will be compared between groups. Changes in pain will be evaluated for individual subjects and compared between groups. For each subject, mean pain scores over the first and second months following TFA or TTA surgery will be calculated. An overall mean across all subjects will be calculated. Additionally, sub-analyses will be performed to determine if there is a difference in these outcomes between groups over different post-operative phases (such as acute (e.g. days 1-30) or subacute (e.g., 1-3 months), or chronic (e.g. >3 months)). Statistical analysis will be performed with two-sample t-test, and p-values will be reported without adjustment, consistent with feasibility study design and the number of subjects.

Pain medication usage will be recorded in subject diaries and obtained during follow up encounters. Opioid medication use will be analyzed by averaging 24-hour morphine equivalent dosing (MED) over each follow-up interval and comparing groups. Changes in opioid medication use will be reported for individual subjects by calculating morphine equivalent dosing (MED). Average MED will be calculated and compared between groups. The time to cessation of opioid use will be reported. Side effects associated with opioid use will be assessed at each visit and the number of side effects occurring over various intervals will be recorded. Analgesic-related outcomes will be compared between the Groups.

Patient Global Impression of Change (PGIC), Pain Catastrophizing Scale (PCS), and Pain Disability Index (PDI) scores will be averaged for each group and compared. Data regarding functional outcomes (Functional Independence Measure [FIM] score), time to wound healing, incidence of neuromas, prosthesis fitting, time to hospital discharge, 30-day readmission rate, and hospital discharge survey will be compared between groups.

7.0 Risks and Benefits

7.1 Potential Benefits

It is possible that subjects in this study may not receive any direct benefit from their participation in this study. If the investigational treatment is successful, subjects in the Treatment Group may have a reduction in acute post-amputation pain, decreased probability of developing chronic post-amputation pain, less interference due to pain, decreased opioid medication use, increased tolerance for rehabilitation and accelerated functional improvement. This research may benefit future patients with post-operative pain following TFA or TTA.

7.2 Potential Risks

The devices used in this study have been cleared by the United States Food and Drug Administration to provide postoperative analgesia. Potential risks include infection, lead fracture, lead migration and/or dislodgement, nerve injury, bleeding, skin irritation, increased pain, and discomfort on insertion, during use or with withdrawal. However, there may be other risks that are currently unknown. The incidences provided are all estimated except for lead fracture. The risks listed below are described as either common (occurring more than 10% of the time), uncommon (occurring about 2-10% of the time), or rare (occurring less than 1% of the time).

7.2.1 Infection

Based on previous studies using this PNS system, the risk of infection is rare. When compared to continuous femoral nerve block and/or continuous sciatic nerve blocks, the risk of infection from a percutaneously placed lead near these nerves is expected to be lower. The risk is thought to be mitigated by the inherent structure and design of the lead. Unlike nerve block catheters, PNS leads do not have an internal conduit through which bacteria can enter the body. The coiled structure of the fine wire lead allows it to stretch when pulled, rather than move into or out of the insertion site. This is thought to minimize the potential of introducing bacteria into the body. Lastly, the electrode is designed to have a tight electrode-skin barrier to help prevent bacterial inoculation. Infection risk will be minimized by using sterile leads and thoroughly cleansing the insertion site with antibacterial solution at the time of insertion. The insertion site will be covered with a dressing to keep it clean and dry, and the subjects will be instructed to inspect the site for signs of infection or irritation regularly and to inform the investigator if they occur. If infection occurs, the investigator may administer an antibiotic and/or remove the lead.

7.2.2 Lead fracture

Lead fracturing beneath the skin is a common risk, with most or all fractures occurring during the procedure to remove the lead. When this occurs, one or more lead fragments may remain in the body. Granuloma (mild tissue inflammation) is directly related to the risk of retained electrode fragments. The investigators will inspect the lead after removal to determine if any fragments were retained in the body. If there is suspicion of a retained fragment, the investigator will determine if removal of the lead is medically necessary. In most cases, removal is not necessary unless there are further sequalae associated with the fragment, such as infection or granuloma. Retained fragments may also be removed if the subject desires. The impact of retained fragments *in situ* is minimal and in most cases, retained fragments do not need to be removed.

7.2.3 Lead migration and/or dislodgement

It is possible for a lead to migrate from its original position or become dislodged (i.e. entirely removed from the insertion site) during the 30-day treatment period. This is a common risk. If migration occurs, the subject may experience discomfort during stimulation. Stimulation near the skin surface may be perceived

as “pins and needles” which may be uncomfortable to the subject. Please see below for the steps taken cases of discomfort associated with the PNS system. In cases of significant migration or complete dislodgement, a replacement lead may be inserted depending on the desires of the patient and time remaining in the treatment period.

The risk of lead migration or dislodgement is reduced by providing instructions to the subject and their caregiver, as appropriate, to ensure careful handling of the lead and lead connector during bandage changes. Discomfort or pain due to stimulation may occur if the lead migrates from its original location. Stimulation near the skin surface may be perceived as a “pins and needles” sensation and may be uncomfortable. Stimulation parameters or a new lead may be placed if necessary for additional comfort. A tingling sensation may be felt under the pad but this sensation is not expected to be uncomfortable.

7.2.4 Nerve injury

The risk of mechanically damaging a nerve with the introducer is rare and will be mitigated by using ultrasound to visualize the nerves, surrounding landmarks, and relative position of the introducer. Though the lead placement procedure is like the procedure used for regional anesthesia nerve blocks, the lead can be placed further away from the nerve when compared to placement of nerve block catheters. The risk of nerve injury may be further reduced by proper subject positioning and slow advancement of the introducer, stopping approximately 0.5 – 3 cm proximal to the nerve.

7.2.5 Bleeding

The risk of bleeding from lead placement is rare and is expected to be no greater than the risk of bleeding related to peripheral nerve block catheters. INR for anticoagulated patients will be available for review as patients undergoing surgery will have this checked as a part of routine pre-operative assessment.

7.2.6 Skin irritation

It is a common risk for skin to become irritated at the lead exit site, under the stimulator pad (a modified surface electrode that is positioned between the skin and the stimulator device), in the area surrounding the lead insertion site, and at the site where an adhesive bandage and lead connecter are taped to the skin. Skin irritation is reduced by excluding patients with known sensitivity to skin-contact materials (stickers, bandages, tape etc.). Subjects and their caregivers will be advised to examine the electrode exit site at regular intervals to look for any signs of irritation. To avoid irritation under the pad and lead connector tape, subjects will be advised that the stimulator and pad may be moved to various locations near the lead insertion site throughout the study. To avoid irritation under the belt, subjects will be instructed to move the belt as needed. In addition, subjects will be instructed to avoid placing the pad, belt, lead connector tapes, or bandages on unhealthy skin.

7.2.7 Discomfort or increased pain on insertion, during use or with withdrawal

Like procedures involving percutaneously inserted needles (e.g., injections, needle electromyography, acupuncture), discomfort associated with test stimulation/placement of the stimulator lead is possible. Usually the discomfort is transient and improves shortly after needle insertion. Subjects are asked to provide feedback on pain or discomfort experienced during the procedure. Symptomatic relief with local anesthesia may be used to reduce discomfort.

Electrical stimulation is perceived by the subject as tingling or vibratory sensations. These sensations are expected to be comfortable, however it is possible that they can cause discomfort or pain. Uncomfortable sensations are likely directly related to stimulus intensity, which is adjusted on the PNS stimulator. Pain is typically associated with higher intensity levels. During the lead placement procedure, stimulus intensity is adjusted to the determine the minimum and maximum range of intensities that produce comfortable

sensations without discomfort or pain. Prior to completion of the lead placement procedure, an appropriate stimulation intensity is set. Further, the subject can select from a range of intensities determined by the investigators as safe and unlikely to cause discomfort. If a subject ever feels pain related to stimulation, they can turn down the intensity or turn the stimulator off.

Subjects may experience worsening of pain symptoms or may not obtain any therapeutic benefit from the system. Worsening pain could be caused by natural changes in pain during post-operative recovery and rehabilitation, or may be caused by electrical stimulation, or the presence of the lead. This is a common risk, but worsening pain is expected to be transient, resolving without additional treatment. Subjects can have their stimulation parameters adjusted throughout the study for optimal comfort, or treatment may be discontinued. These risks are mitigated by clinical training on the safe limits of stimulation and the proper placement of the leads.

7.3 Risk-Benefit Analysis

All efforts will be made to reduce the incidence of the potential risks described above. Despite taking all necessary precautions, these events, as well as unanticipated events may still occur. All procedures will be performed by trained attending physicians working within their scope of practice. Practices will be maintained to mitigate the potential risks discussed above. If an event occurs, the potential for significant harm is low because the risks presented have non-serious consequences. Further, the subjects in the Treatment Group may gain no direct benefit from electrical stimulation. This investigation has inherent risks to Treatment Group subjects which are justifiable based on the following rationale:

The insertion of needles targeting the femoral or sciatic nerves carries the risk of damaging unintending structures including nerves, blood vessels, organs, and joint spaces. The risk of damage to these structures is reduced by utilization of ultrasound guidance, knowledge of anatomic landmarks, and awareness of needle position and depth. The physicians performing placement of the PNS system are trained in regional anesthesiology with experience in the placement of peripheral nerve block catheters or will receive the appropriate training necessary to safely conduct the procedure. Lead placement for the peripheral nerve stimulator requires a needle distance that is further from the target nerve than does placement of a peripheral nerve block catheter (5 – 30 mm and 2 mm, respectively). The increased distance between target nerve and needle should lower the risk of injury to unintended structures. Further, evoked responses to electrical stimulation are used to guide lead placement (i.e. the needle is advanced slightly; once stopped, stimulation is applied and the subject is evaluated for responses; process is repeated as needed). If damage to a nerve occurs from direct mechanical injury or nerve compression secondary to hematoma, symptoms are expected to occur within 24-48 hours. Subjects are instructed to contact study personnel if any changes in medical status occurs.

The risk of irritation or infection from needle insertion is reduced by cleaning the lead insertion site using aseptic technique, sterile test needles, and lead introducer needles. Needles are not reused. Subjects with systemic infection and/or immunosuppressive disorders will be excluded. Subjects are instructed to contact study personnel in case of any change in medical status.

The risk of discomfort associated with needle insertion or electrical stimulation are possible. Discomfort arising from needle insertion is usually transient and resolves shortly after needle insertion. Subjects are asked to provide feedback regarding sensations, pain, or discomfort experienced during the lead placement procedure and throughout the study. The test needle and lead introducer needle can be repositioned as necessary to obtain the most comfort. Local anesthetic will be used as needed to reduce discomfort during the procedure. Stimulation parameters can be adjusted throughout the study to obtain the most comfort.

Lead fracture and subsequent retention of lead fragments is possible. Study personnel will inspect the lead upon removal to look for signs of fracture. Usually, no treatment is required for retained fragments unless an infection or granuloma occurs. The study investigators will determine the most appropriate course of treatment.

The potential benefits expected from successful treatment include reduction in pain intensity after TFA or TTA surgery in the acute post-operative setting, decrease in the incidence and/or severity of chronic post-amputation PLP or RLP, reduction in opioid medication use, increased tolerance for rehabilitation and faster functional recovery. This research may benefit future patients with post-operative pain following TFA or TTA. Additionally, the PNS system used in this study has not been formally investigated to be used in the acute post-operative setting after TFA or TTA. Information regarding its efficacy and utility in this setting may be useful in determining the most appropriate applications for this system in the future. The potential risks associated with the use of this PNS system have non-serious consequences and are expected to be uncomplicated to manage. The risks are justifiable by the potential benefits. The information to be gained in this study may be used to refine further research within the area of peripheral nerve stimulation for the management of post-operative pain.

8.0 Data and Safety Monitoring

Primary and secondary outcomes will be recorded at each follow-up visit. Study investigators will retain study-related documents in double-locked filed cabinet in 2C-117. The PI or an investigator will conduct a data and safety monitoring review once every 8 weeks in which Case Report Forms and any AE forms are evaluated. Safety information is also assessed at outpatient study visits and by telephone calls. If study investigators determine that the PNS treatment is unsafe to continue (i.e. systemic infection, increased pain that is intolerable to the subject, need for implantable electronic device that requires discontinuation of the PNS), then PNS will be discontinued as appropriate.

8.1 Serious Adverse Events

Serious Adverse Events (SAE) will be recorded on Form AE and the IRB will be notified within 5 days of occurrence. Monitoring for SAEs will occur at each follow-up encounter. Subjects will be asked if they are experiencing any increased discomfort, pain, skin irritation, or bleeding. At the outpatient follow-up visits, the PNS lead exit site will be examined and the stimulator device will be interrogated to ensure proper functioning. Any adverse event will be investigated and managed as appropriate. Subjects are instructed to notify study personnel by telephone (804-675-5188) in case of any changes in medical status as soon as possible. If investigators need to be reached after normal business hours, subjects will be given instructions on how to page study staff who call the subject as soon as possible.

Details regarding any observed adverse event and its relation to the PNS system will be collected on Form AE. The severity of the AE 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 treatment necessary related to the AE will be documented. AEs will be followed to resolution, even if a subject is discharged from the study early. Adverse events will be documented and reported so that the safety profile of this system may be further understood.

8.2 Confidentiality

All subjects who sign a Consent Form will be asked to provide name, social security number, and date of birth. We will use this information to create a “unique identifier” to protect patient confidentiality. The

unique identifier will be used in place of the subjects' names for all data collection forms and study databases. A master list linking the subjects to the unique identifier will be maintained by study investigators in 2C-117. The number of subjects to be enrolled does not include screen failures. A record will be maintained of all subjects that are screened at the Vascular Clinic. A Subject Identification log will be completed for all subjects enrolled in the study. Information pertaining to subjects are accessible by study personnel in the electronic medical record. Information to be collected includes age, race, gender, height, weight, past medical and surgical history, and eligibility criteria will be assessed as outlined in Form 00. Preliminary screening will be used to determine a subject's eligibility for study participation. All patient sensitive information, study related documents and materials will be stored in a secured, locked cabinet in 2C-117.

The protection of patient confidentiality is of utmost importance. Subject names and personal identifiers will not appear in any publications resulting from this research. Subjects will be informed that the IRB and regulatory authorities will have access to records that identify them as individuals. All applicable HIPAA regulations will be followed.

9.0 Consultants

Non-sensitive data resulting from this study will be made available to Robert Litwack, M.D. for assistance with data analysis. Outcome measures (e.g. pain scores and patient survey scores) without sensitive identifying information will be communicated to Dr. Litwack via VA regulated email and Safe Access File Exchange (SAFE) to ensure secure transmission of study information. Data will be transmitted at various periods during the study and a final data set will be created at the end of the study duration.

Nate Crosby, Ph.D. of SPR Therapeutics has assisted with protocol development. His research background as well as knowledge of the SPRINT PNS System and ongoing studies with the device in chronic post-amputation pain and total knee arthroplasties has been important to the development of this protocol. He will assist in training the study investigators in placement of the device. He will continue to provide advice during the study as needed.

10.0 Appendix

Schedule of Study Procedures

	Visit		1	2	3	4	5	6	7	8	9	10	11	12	13
		Screen and Consent	Baseline	Lead placement (Group 1 only)	1 week PNS	2 weeks PNS	3 weeks PNS	4 weeks PNS/1st IPC evaluation	5 weeks PNS	6 weeks PNS	7 weeks PNS	8 weeks PNS/2nd IPC evaluation	3 month phone	6 month phone	12 month phone
	Chart Review/Screening	x													
Study Procedure	Informed Consent	x													
	Remove PNB catheter	x													
	Beck Depression Inventory	x													
	Randomize		x												
	Lead Placement			x											
	Start Stimulation			x											
	Inspect bandages and Lead exit site			x				x				x			
	Remove Lead											x			
	Assess AEs				x	x	x	x	x	x	x	x	x	x	x
Pain/Sense	BPI-2 (pain distribution)		x												
	BPI-3 (worst pain)		x		x	x	x	x	x	x	x	x	x	x	x
	BPI-4 (least pain)		x		x	x	x	x	x	x	x	x	x	x	x
	BPI-5 (average pain)		x		x	x	x	x	x	x	x	x	x	x	x
	Phantom sensation		x		x	x	x	x	x	x	x	x	x	x	x
Meds/SE	Opioid-related side effects		x		x	x	x	x	x	x	x	x	x	x	x
	Pain medications		x		x	x	x	x	x	x	x	x	x	x	x
	BPI-9 (interference)		x					x				x	x	x	x
	PGIC							x				x	x	x	x
	PCS		x					x				x	x	x	x
	PDI		x					x				x	x	x	x
	FIM		x					x				x	x	x	x
	Time to prosthesis fitting	Data collected from medical record													
	Time to hospital discharge	Data collected from medical record													
	Hospital discharge survey	Data collected from medical record													
	30-day readmission rate	Data collected from medical record													
	Incidence of neuromas	Data collected from medical record													

Literature Cited

1. Richardson et al. A prospective study of factors associated with the presence of Phantom limb pain 6 months after major lower limb amputation in patients with peripheral vascular disease The Journal of Pain Volume 8, Issue 10, October 2007, Pages 793–801.

2. Hanley M, et al. Pre-amputation pain and acute pain predict chronic pain after lower extremity amputation The Journal of Pain Vol 8, Issue 2, Feb 2007, pg 102-109.

3. Liu SS et al. Prolonged Postoperative Pain in Total Knee and Total Hip Arthoplasty Reg Anesth Pain Med 2012; 37-42.

4. Hickey OT et al. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain Clin J Pain 2010; 26: 556-560.

5. Apfelbaum et al. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged Anesth Analg. 2003 Aug;97(2):534-40.

6. Wilson RD et al. Peripheral Nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: a RCT Am J Phys Med Rehabil, 2014. 93(1): p. 17-28.

7. Rauck RL et al. Treatment of Post amputation pain with peripheral nerve stimulation Neuromodulation: Journal of the International Neuromodulation Society, 2014. 17(2): p. 188-97.

8. Kent ML et al. Perioperative Pain Management Strategies for Amputation: A Topical Review. Pain Medicine, 2016; 0: 1-16.

9. Ilfeld et al. Ultrasound-Guided Percutaneous Peripheral Nerve Stimulation for Postoperative Analgesia. Reg Anesth Pain Med 2016;41: 00–00.

10. Ehde DM, Czerniecki JM, Smith DG et al. Chronic phantom sensations, phantom pain, residual limb pain, and other regional pain after lower limb amputation. Arch Phys Med Rehabil 2000;81:1039–1044.

11. Sherman RA, Sherman CJ. Prevalence and characteristics of chronic phantom limb pain among American veterans: Results of a trial survey. Am J Phys Med 1983;62(5):227–38.

12. Kooijman CM, Dijkstra PU, Geertzen JH, Elzinga A, van der Schans CP. Phantom pain and phantom sensations in upper limb amputees: An epidemiological study. Pain 2000;87(1):33–41.

13. Whyte AS, Carroll LJ. A preliminary examination of the relationship between employment, pain and disability in an amputee population. Disabil Rehabil 2002;24:462–470

14. Sherman RA,Sherman CJ,Gall NG.A survey of current phantomlimb pain treatment in the United States. Pain 1980;8:85–99.

15. Ilfeld BM, Duke KB, Donohue MC. The association between lower extremity continuous peripheral nerve blocks and patient falls after knee and hip arthroplasty. Anesth Analg. 2010;111:1552–1554.

16. Capdevila X, Bringuier S, Borgeat A. Infectious risk of continuous peripheral nerve blocks. Anesthesiology. 2009;110:182–188.

17. Huntoon MA, Hoelzer BC, Burgher AH, Hurdle MF, Huntoon EA. Feasibility of ultrasound-guided percutaneous placement of peripheral nerve stimulation electrodes and anchoring during simulated movement: part two, upper extremity. Reg Anesth Pain Med. 2008;33:558–565.

18. Huntoon MA, Huntoon EA, Obray JB, Lamer TJ. Feasibility of ultrasound-guided percutaneous placement of peripheral nerve stimulation electrodes in a cadaver model: part one, lower extremity. Reg Anesth Pain Med. 2008;33:551–557.

19. Huntoon MA, Burgher AH. Ultrasound-guided permanent implantation of peripheral nerve stimulation (PNS) system for neuropathic pain of the extremities: original cases and outcomes. Pain Med. 009;10:1369–1377.

20. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150: 971–979.

21. North R.Spinal cord and peripheral nerve stimulation: technical aspects. In:Simpson BA, ed. Electrical stimulation and the relief of pain.New York: Elsevier, 2003:183–195.

22. Rauck RL, Kapural L, Cohen SP et al. Peripheral nerve stimulation for the treatment of post-amputation pain—a case report. Pain Pract 2012;12:649–655.

23. Karanikolas, M, Aretha, D, Tsolakis, I, Monantera, G, Kiekkas, P, Papadoulas, S, Swarm, RA. Optimized perioperative analgesia reduces chronic phantom limb pain intensity, prevalence, and frequency. Anesthesiology: 2011; 114: 1144-1154.

24. Ziegler-Graham K1, MacKenzie EJ, Ephraim PL, Travison TG, Brookmeyer R. Estimating the prevalence of limb loss in the United States: 2005 to 2050. Arch Phys Med Rehabil. 2008 Mar;89(3):422-9.

25. Dillingham TR1, Pezzin LE, MacKenzie EJ. Limb amputation and limb deficiency: epidemiology and recent trends in the United States. South Med J. 2002 Aug;95(8):875-83.