



TO: FILE (Protocol 0122-CSP-001, NCT 01094301)

FROM: SPR Therapeutics, INC

DATE: July 25, 2018

RE: Conversion from LLC to Corporation and Registration of SPR

The attached protocol (0122-CSP-001) for the NCT study number 01094301 was last revised in February of 2017. 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 SPR System® trademark for the device mentioned in the protocol has registered with the USPTO.

A Prospective Multicenter Pilot Study of the SPR™ System for the Treatment of Post-Stroke Shoulder Pain

Sponsor: SPR Therapeutics, LLC
Cleveland, OH USA

Study Responsibility: Maria Bennett, MS
CEO
SPR Therapeutics
22901 Millcreek Boulevard
Suite 110
Cleveland, OH 44122
Phone: 216-378-9106
Fax: 216-378-9116

IDE Number: IDE G090085 (Approved)

Study Centers: Weill Cornell Medical College
Albert Einstein Healthcare Network/MossRehab
Carolinas Healthcare/Charlotte Institute of Rehabilitation
MetroHealth Medical Center

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CONFIDENTIAL INFORMATION

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

Protocol Synopsis

Title	A Prospective Multicenter Pilot Study of the SPR™ System for the Treatment of Post-Stroke Shoulder Pain
Indication	The SPR System is intended for the reduction of post-stroke shoulder pain for patients who are unresponsive to or cannot tolerate conventional therapy (medications, slings, etc.)
Investigational (Test) Device	The SPR™ (<i>Stimulation for Pain Relief</i>) System
Study Design	Prospective Multicenter Case Series Study
Primary Study Objective	To gather preliminary data on the safety, clinical efficacy, and performance of the SPR System for the treatment of post-stroke shoulder pain.
Study Plan	<p>Subjects with chronic (≥ 6 months) post-stroke shoulder pain rated as ≥ 4 on the Brief Pain Inventory pain intensity question (Question #3) will receive the first stage of the SPR System. The SPR System is a two-staged neurostimulation therapy which delivers stimulation to the [REDACTED] shoulder. The first stage (SPR Trial Stage) uses a temporary [REDACTED] Lead placed percutaneously [REDACTED] and a body-worn external stimulator (the Smartpatch Stimulator). Subjects meeting the specified success criteria at the conclusion of the SPR Trial Stage who then experience a return of pain within 6 months of completion of the Trial Stage will be consented and screened for eligibility for the second stage (SPR Implant Stage). A “return of pain” is defined as: 1) an increase in pain by at least 2 points compared to the end of Trial Stage (Visit 5) pain score; and 2) BPI Question #3 score of at least 4 (both criteria must be met for at least 2 weeks). The SPR Implant Stage uses an Implantable Pulse Generator (IPG) and an Implantable [REDACTED] Lead.</p> <p>Subjects will be permitted to continue use of non-opioid analgesic medications throughout the study; however, dosages of these medications will be controlled during the study. Subjects will be permitted to reduce or maintain their dosage of non-opioid analgesic medications, however, they will be asked to not increase their dosage of these medications above their baseline dosage during the week prior to each study visit and scheduled telephone call (and during the six month Trial Stage follow-up period). Subjects will not be permitted to continue use of opioid analgesic medications (except as needed in the week immediately following the Implant Stage procedure for post-surgical pain management), to receive injections to the affected limb, or to use slings or other stabilization devices/methods during study participation. Subjects who require concurrent physical or occupational therapy for shoulder pain will be excluded.</p> <p>Subjects will use the Smartpatch System for 6-weeks during the Trial Stage. To evaluate the placebo effect, the first 3-weeks of the SPR Trial Stage consist of a sham period in which the SPR Trial Stage system (i.e., the Smartpatch System) is placed, but stimulation is not delivered. Subjects will be blinded to the fact that stimulation is not being delivered. Following the sham period, stimulation will be turned on, and subjects will receive stimulation for a total of 6 hours per day for 3 weeks. Subjects will be queried for pain intensity on a weekly basis during the SPR Trial Stage using the BPI Short Form Question #3 (BPI3), and subjects will be instructed to focus on their shoulder pain when answering the BPI. At the end of the sham period, pain intensity will be compared to baseline pain intensity scores to evaluate the effect of sham stimulation. At the conclusion of the SPR Trial Stage, subjects achieving at least a 2-point reduction on the BPI3 will be Trial Stage successes. These subjects will receive monthly follow-up calls in order to determine eligibility to advance to the SPR Implant Stage. During the</p>

	<p>Implant Stage, subjects will receive the fully implantable SPR Implant Stage system and be followed for 3 years.</p> <p>All primary and secondary endpoints will be assessed at baseline and again at the completion of the sham period and the active stimulation period of the SPR Trial Stage. In addition, primary endpoints will be evaluated via monthly phone calls during the Trial Stage follow-up period as well as at visits during the SPR Implant Stage (3-weeks, 6-weeks, 12-weeks, 6-months, 9-months, and 12-months post IPG Stim ON). In addition, long-term follow-up will be conducted on an annual basis at 24-months and 36-months post IPG Stim ON.</p> <p>Primary efficacy of the Trial Stage will be determined at the end of the Trial Stage. Primary efficacy of the Implant Stage will be determined at 12-weeks post IPG Stim ON. All Implant Stage subjects will continue to be evaluated at 6, 9, and 12-months post IPG Stim ON follow-up visits and annually for 36 months to determine the long-term efficacy and safety profile of the SPR Implant System and to evaluate the effect of dosage (number of hours of use each day) on treatment effect. Adverse events will be assessed at all follow-up visits.</p>
Number of Sites	Up to 5 Investigational Sites will be enrolled
Number of Subjects	45 subjects will participate in the SPR Trial Stage. Although we expect to yield approximately 18 subjects with an implantable system (SPR Implant Stage), all eligible Implant Stage subjects will be permitted to advance to the Implant Stage.
Inclusion Criteria	<ul style="list-style-type: none"> • At least 21 years old • ≥ 6 months after the stroke that caused shoulder pain • Subject failed or did not tolerate at least two conservative therapies for a total period of at least 6 months since the onset of post-stroke shoulder pain. • Shoulder pain as indicated by a score of ≥ 4 on the Brief Pain Inventory Short Form Question 3 (BPI3) • Upper extremity hemiplegia (no shoulder abduction, shoulder abduction in synergy, or if isolated movement is present, Medical Research Council (MRC) grade $\leq 4/5$) • Cognitive ability to fulfill study requirements based upon a score of ≥ 24 on the Mini Mental Status Exam (MMSE) • Ability to appropriately rank pain on a Numeric Rating Scale (based upon the Investigator's determination of the subject's ability to rank pain) • Availability of a reliable adult who can check the skin and assist the subject with the study protocol requirements • Able and willing to take part in study and comply with all study requirements
Additional Inclusion Criterion for Implant Stage	<p>In addition to continuing to meet the above inclusion criteria (with the necessary pain score already having been confirmed at a Trial Stage Follow-up Call), subjects must:</p> <ul style="list-style-type: none"> • Be a Trial Stage Success AND • Have a clinically significant return of pain as defined by an increase in BPI3 score of at least 2 points (compared against the BPI3 score at Visit 5) resulting in a BPI 3 score of at least 4 within 6 months of the end of the Trial Stage that is sustained for at least two consecutive weeks.
Exclusion Criteria	<ul style="list-style-type: none"> • Evidence of joint or overlying skin infection of the affected limb • Taking opioid medication (or Tramadol) for shoulder pain OR for any other chronic pain condition

	<ul style="list-style-type: none"> • Intra-articular or sub-acromial steroid injections or botulinum toxin injections to the affected shoulder in the previous 12 weeks • History of arrhythmia with hemodynamic instability, such as ventricular tachycardia, supraventricular tachycardia and rapid ventricular response atrial fibrillation OR valvular heart disease including artificial valves • Evidence of non-stroke related shoulder pathology with continuing symptoms (such as pathology related to a traumatic injury, tumor, or infection) • Bleeding disorder OR INR >3.0 for those on warfarin • Unable, per the prescribing physician, to stop antiplatelet medications [e.g., aspirin, clopidogrel (Plavix)] and/or anticoagulants for at least 7 days prior to SPR implantation • Receiving outpatient physical or occupational therapy for shoulder pain • History of recurrent skin infections • Compromised immune system based upon medical history (i.e., HIV/AIDS, actively taking or recently completed immunosuppressive therapies such as chemotherapy or radiation of the head/neck, congenital immunodeficiency, or any other cause for compromised immune system documented in the medical history) • Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator • Severely impaired communication skills (receptive or expressive) as determined by the Investigator • Confounding conditions such as ipsilateral upper limb lower motor neuron lesion, Parkinson's Disease, SCI, traumatic brain injury, MS, or complex regional pain syndrome • Uncontrolled seizures (>1 per month for 6 months) • An implanted electronic device • Allergy to skin surface electrodes and/or medical-grade adhesive tapes • Allergy to local anesthetic agents such as lidocaine or previous reaction to Monitored Anesthesia Care (MAC) • Pregnant • Prisoners, minors, legally incompetent people, unconscious patients, house staff, or students
Primary Safety Endpoint	<ul style="list-style-type: none"> • Occurrence of device-related adverse events.
Primary Clinical Endpoint	<ul style="list-style-type: none"> • Trial Stage Success <ul style="list-style-type: none"> ○ Statistically significant proportion of subjects achieving at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the end of the Trial Stage (Visit 5) relative to end of the placebo period or baseline (Visit 4 or Visit 1), whichever is lower OR reporting a BPI3 score of zero at the end of the Trial Stage. • Implant Stage Success <ul style="list-style-type: none"> ○ Statistically significant proportion of subjects participating in the Implant Stage achieving at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the 12-week post-IPG stim on visit (Visit 10) relative to end of the placebo period or baseline (Visit 4 or Visit 1), whichever

	is lower OR reporting a BPI3 score of zero at the 12-week post-IPG stim on visit.
Secondary Endpoints	<ul style="list-style-type: none"> • Pain <ul style="list-style-type: none"> ○ BPI Pain Interference Question (BPI9) ○ Pain-free passive range of motion • Quality of Life <ul style="list-style-type: none"> ○ Medical Outcomes Study Short Form (SF-36v2) • Global impact of stimulation therapy <ul style="list-style-type: none"> ○ Patient Global Impression of Change (PGIC) scale • Emotional functioning <ul style="list-style-type: none"> ○ Beck Depression Inventory Second Edition (BDI-II) • Device Performance and User Satisfaction of SPR System • Changes in Quantitative Sensory Testing (QST) thresholds • Impact of Therapy on Arm Impairment using the Stroke Upper Limb Capacity Scale (SULCS) • Economic Impact of Shoulder Pain at Baseline

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1.0 GENERAL INFORMATION

1.1 Title of Investigation

A Prospective Multicenter Pilot Study of the SPR™ System for the Treatment of Post-Stroke Shoulder Pain

1.2 Sponsor Name and Address

SPR Therapeutics, LLC
22901 Millcreek Boulevard
Suite 110
Cleveland, OH 44122

Phone: 216-378-9106

Fax: 216-378-9116

1.3 Name of the Investigational Device

The SPR™ (*Stimulation for Pain Relief*) System

1.4 Intended Use

The SPR System is intended for the reduction of post-stroke shoulder pain for patients who are unresponsive to or cannot tolerate conventional therapy (medications, slings, etc.).

1.5 Study Objective

Shoulder pain is a common complication following stroke, affecting almost one third of stroke survivors (Lindgren et al., 2007). Of the multitude of treatment options, only surface electrical stimulation has been reported to be effective in multiple randomized controlled trials (Baker and Parker, 1986; Chantraine et al., 1999) and has been recommended by clinical practice guidelines (Teasell et al., 2003; Bates et al., 2005). Electrical stimulation therapy is a promising treatment option; however, clinical and technical difficulties associated with surface stimulation, such as discomfort caused by stimulation of cutaneous pain receptors and the need for skilled personnel to place the surface electrodes on a daily basis, have prevented it from becoming the standard of care. Percutaneous [REDACTED] electrical stimulation for the treatment of post-stroke shoulder pain was first attempted because of experience with patients being unable to tolerate the pain of surface stimulation for more than a few seconds at a time (Chae et al., 2001). Improvements were reported in quantitative measures of pain, and this case report provided the first evidence to support the use of percutaneous, [REDACTED] electrical stimulation for the treatment of post-stroke shoulder pain. Subsequent controlled studies (Yu et al., 2004, Chae et al., 2005) demonstrated the greater efficacy of percutaneous [REDACTED] stimulation compared to controls, [REDACTED]

We propose that a miniature, minimally invasive, 2-stage system will reduce pain as effectively as prior electrical stimulation systems, while offering significant

practical advantages that will make electrical stimulation therapy for post-stroke shoulder pain clinically viable. Based on prior studies and experiences, we have developed a system that will provide comfort, patient compliance, ease of therapy delivery, and long term pain relief.

The objective of this multicenter pilot study is to acquire preliminary clinical safety and effectiveness data, and to gain performance data using the SPR System. In this pilot study, we propose to evaluate the clinical and technical performance of using one percutaneous Smartpatch Lead placed [REDACTED] for the reduction of post-stroke shoulder pain that is then replaced with an Implantable Lead for subjects experiencing a return of pain after short-term therapy. We also propose to evaluate the placebo effect through sham stimulation during the first 3-weeks of the SPR Trial Stage. Those subjects responding sufficiently to the second 3-weeks of active percutaneous stimulation in the SPR Trial Stage who subsequently report a return of pain that is sustained for two consecutive weeks will receive an implantable system in the SPR Implant Stage.

At the conclusion of this pilot study, we will be able to assess if the SPR System using a single [REDACTED] Lead [REDACTED] is clinically and technically successful. If successful, information gained from the conduct of this study will provide meaningful clinical and technical information for the design of a larger pivotal study on the implantable system in support of a marketing application for the 2-stage system.

2.0 INTRODUCTION AND BACKGROUND

2.1 Introduction

As stated above, clinical and technical difficulties associated with surface stimulation, such as discomfort caused by stimulation of cutaneous pain receptors and the need for skilled personnel to place the surface electrodes on a daily basis, have prevented it from becoming the standard of care.

[REDACTED] electrical stimulation is a promising treatment alternative. [REDACTED] electrical stimulation is significantly better tolerated than surface stimulation (Yu et al., 2001b). Insertion of leads [REDACTED] bypasses cutaneous pain receptors and ensures stable electrode placement. Further, once placed, skilled personnel are not needed on a daily basis to place surface electrodes to ensure reliable and effective [REDACTED]. A multicenter randomized clinical trial demonstrated the effectiveness of [REDACTED] electrical stimulation system in reducing post-stroke shoulder pain (Yu et al., 2004, Chae et al., 2005).

[REDACTED]

We believe that the placement of one lead [REDACTED] [REDACTED] is less invasive and will be sufficient to provide similar therapeutic benefit, while providing significant clinical and technical advantages, such as shorter procedure time, reduced number of lead insertions, and fewer lead exit sites to maintain. We will evaluate the single lead approach during this pilot study.

In the previous percutaneous [REDACTED] stimulation multicenter clinical trial, a four lead system was used. The four leads stimulated [REDACTED]. This study's original objective was to reduce inferior shoulder subluxation by stimulating [REDACTED]. Ultimately, study results demonstrated that subjects had a significant reduction in shoulder pain regardless of the degree of subluxation reduction, and that the pain reduction was the outcome that was most clinically significant to the patient and clinician. This study concluded that [REDACTED] stimulation significantly reduced post-stroke shoulder pain, and in some subjects reduction of subluxation may have contributed to the pain reduction [REDACTED].

[REDACTED]. A small study conducted by the principal investigators confirmed these findings and concluded that stimulation of the [REDACTED] did not result in subluxation reduction or improve subluxation reduction when stimulated in combination with other muscles, again suggesting that [REDACTED] were responsible for the therapeutic benefit (Yu et al, 1998). Finally, according to our clinical advisors, the majority of post-stroke patients identify the area of the [REDACTED] [REDACTED] as the painful region of their shoulder. Thus, we propose that a system using a single lead [REDACTED], [REDACTED].

The Sponsor, SPR Therapeutics, proposes to evaluate the clinical and technical feasibility of using a single Lead to deliver [REDACTED] stimulation for the treatment of post-stroke shoulder pain. This evaluation is a prospective non-randomized case series study of the SPR System. The SPR System is a two-staged neurostimulation therapy which delivers stimulation [REDACTED]. The first stage (SPR Trial Stage) involves the use of a body-worn external stimulator (the Smartpatch PNS Stimulator) and a temporary [REDACTED] Lead placed percutaneously [REDACTED]. Subjects meeting the success criteria for the SPR Trial Stage who, within 6 months, experience a return of pain that is sustained for two consecutive weeks will progress onto the second stage (SPR Implant Stage). The SPR Implant Stage involves the use of a fully Implantable Pulse Generator (IPG) and an Implantable [REDACTED] Lead.

Participation in the study will be offered to individuals with post-stroke shoulder pain who are at least 6 months post-stroke and who meet all eligibility criteria. Subjects with chronic post-stroke shoulder pain rated as four or greater on the Brief Pain Inventory worst pain intensity question #3 (BPI3) will be eligible to receive the SPR Trial Stage System.

The SPR Trial System will be placed by Physical Medicine and Rehabilitation Physicians (Physiatrists) who are experienced in the placement of percutaneous leads and/or EMG needle recording electrodes. Surgeons will perform the SPR Implant Stage Procedure.

2.2 Background and History of Shoulder Pain Treatment

A discussion of the currently available options for the treatment of post-stroke shoulder pain, including surface stimulation, as well as the results of studies using [REDACTED] stimulation are presented below.

2.2.1 Post-stroke shoulder pain is a major rehabilitation problem

The American Heart Association estimated that the prevalence of stroke in adults in 2005 was 5.8 million, with an additional 630,000 people surviving a stroke each year (AHA Heart Disease and Stroke Statistics, 2008). Shoulder pain is a common complication following stroke. A recent prospective population-based study on first-time stroke patients found that almost one third of patients developed shoulder pain, most (approximately 79%) describing their pain as moderate to severe, as indicated by a score between 40 and 100 (out of a possible 100) on a visual analog scale (Lindgren et al., 2007).

The treatment of shoulder pain is a crucial step towards recovery for stroke survivors. Shoulder pain has been found to lengthen the time to recovery, produce insomnia, and require additional medications or interventions during rehabilitation (Poulin de Courval et al., 1990). Therapeutic exercises under the supervision of a trained professional are considered to be an important part of post-stroke rehabilitation (Lynch et al., 2005; Gustafsson and McKenna, 2006), but pain can interfere with completing these exercises. Stroke survivors who avoid using the affected arm are less likely to regain motor function, causing long term impairment of functional abilities resulting in a greater dependence on caregivers.

The influence of shoulder pain on daily life was recently evaluated in a prospective study of first-time stroke patients (Lindgren et al., 2007). At four months post-stroke, 23% of patients with shoulder pain reported self-perceived ill health, compared to only 8% of patients without shoulder pain ($p < 0.001$). Additionally, 63% of patients with shoulder pain reported moderate to major dependence on caregivers, compared to 25% of patients without shoulder pain ($p < 0.001$). A significant association has also been found between shoulder pain and depression (Gamble et al., 2000). These physical and psychosocial

consequences of pain contribute to an overall decreased quality of life (Widar et al., 2004).

Though its etiology is poorly understood, there are a variety of conditions that are believed to contribute to post-stroke shoulder pain. Muscle weakness and spasticity of shoulder muscles are common following a stroke and both are believed to be contributing factors for shoulder pain. Lindgren and associates (Lindgren et al., 2007) reported a significant association between lost or reduced arm motor function and shoulder pain. Similarly, Wanklyn and associates (Wanklyn et al., 1996) found that reduced shoulder shrug and the need for assistance during transfers, both indicators of weakness, were associated with shoulder pain. Other studies have found that patients experiencing spasticity are more likely to experience shoulder pain than those experiencing flaccidity (Van Ouwenaller et al., 1986; Poulin de Courval et al., 1990).

Spasticity and weakness are believed to cause mechanical instability and immobility of the glenohumeral joint, which can lead directly to shoulder pain or result in secondary painful conditions such as subluxation, rotator cuff impingement, adhesive capsulitis and complex regional pain syndrome (Sheffler and Chae, 2007). The general consensus is that impaired motor function of the upper limb is the most important contributing factor for shoulder pain (Gamble et al., 2002; Ratnasabapathy et al., 2003; Lindgren et al., 2007; Wanklyn et al., 1996).

2.2.2 Post-stroke shoulder pain is not adequately addressed by present treatment options

Numerous interventions exist for the treatment of shoulder pain following stroke. This is due to the large number of possible etiologies, the diversity of clinicians that treat stroke patients, and the lack of consensus regarding a standard of care. None of the following interventions have been shown to reduce pain reliably in randomized controlled trials.

Slings and other supports

Arm slings and other mechanical supports, such as wheelchair trays, are often used to support the forearm and distribute its weight to one or both shoulders in an effort to prevent or reduce subluxation. Although slings may reduce subluxation (Brooke et al., 1991; Rajaram and Holtz, 1985), they often fail to reduce shoulder pain as subluxation recurs once they are removed (Hurd et al., 1974; Yu et al., 2004) and may slow rehabilitation by reducing arm mobility.

Strapping

Strapping is the application of non-stretch tape to the affected limb to support the glenohumeral joint while allowing free movement of the arm. In a randomized controlled study of 33 patients, those who received strapping reported reduced average pain compared to those who received no therapy (inactive control group) (Griffin and Bernhardt, 2006). However, strapping fails to produce a significant

benefit compared to active control groups, who received either sham strapping or standard physiotherapy without strapping (Hanger et al., 2000; Griffin and Bernhardt, 2006). In addition, the tapes must be replaced at least every three days, and skin irritation is common (Hanger et al., 2000; Griffin and Bernhardt, 2006).

Local Injection Techniques

Corticosteroid injections address pain by treating inflammation. Approximately 50% of clinicians who treat patients with post-stroke shoulder pain believe that steroid injections are effective (Snels et al., 2000a). However, there are only two randomized controlled trials of corticosteroid injections for the treatment of post-stroke shoulder pain and they have mixed results. A recent trial of subacromial injections reported significant benefit over placebo (Rah et al., 2012). However, an earlier placebo controlled trial of intra-articular injections showed no benefit (Snels et al. 2000b). Post-stroke shoulder pain has a variety of possible etiologies and does not always arise from inflammation, explaining why steroid injections do not consistently outperform placebo in stroke patients (Snels et al., 2000b, Rah et al., 2012). In addition to uncertain efficacy, repeat corticosteroid injections are associated with frequent adverse events (Snels et al., 2000b), making them a poor treatment option.

Botulinum toxin causes local paresis of muscles by blocking cholinergic transmission at the neuromuscular junction. It has been widely used to treat spasticity and some data suggest that it may also help to relieve pain. Six of nine patients in a small uncontrolled study receiving an injection of botulinum toxin to the affected limb reported pain reduction (Bhakta et al., 1996). However, the effect of botulinum toxin is known to diminish after 3-4 months, making repeated injections necessary. Little data exist regarding the repeated use of botulinum toxin for shoulder pain relief.

Oral analgesic medications

The use of opioid and nonopioid analgesics, including nonsteroidal anti-inflammatory drugs (NSAIDs) to manage shoulder pain is common practice (Snels et al., 2000a). Unfortunately, extended use of opioids can lead to dependence and side effects such as headache, skin rash, dizziness, and gastrointestinal symptoms (Van der Windt et al., 1995). Though NSAIDs may reduce shoulder pain in the general population (Van der Windt et al., 1995), their efficacy has not been demonstrated in the stroke population (Green et al., 1998).

Therapeutic exercises

Therapeutic exercises under the supervision of a trained professional are generally considered to be an important part of post-stroke rehabilitation. Although they prevent immobility and improve the range of motion (ROM) of the hemiplegic arm (Lynch et al., 2005; Gustafsson and McKenna, 2006), studies have found that some exercises, such as the use of an overhead pulley, can cause soft tissue damage and thereby worsen shoulder pain (Kumar et al., 1990). In fact, exercises

are generally associated with a worsening of pain or no change, rather than an improvement. In a study investigating static positional stretches, the treatment group showed increasing levels of pain (Gustafsson and McKenna, 2006).

Acupuncture/Electroacupuncture

Acupuncture has been used for centuries to treat various types of pain and is believed to improve cutaneous and muscle blood flow and to increase pain thresholds (Johansson, 1993; Magnusson M et al., 1994; Johansson et al., 1993). Electroacupuncture, a therapy in which traditional acupuncture needles are used in conjunction with electrical stimulation, has been evaluated as a therapy for shoulder pain in post-stroke subjects in a randomized study comparing electroacupuncture plus occupational/physical therapy to therapy alone (Chen et al., 2000). Although statistically significant improvements in pain reported via a Visual Analog Scale were observed in the treatment group, the study did not follow the group beyond the conclusion of the treatment. Thus it is not clear how often the therapy must be reapplied. In addition, electroacupuncture requires repeated clinic visits (at least 3 visits per week for 1 month). Traditional acupuncture has also been evaluated as a treatment for shoulder pain; however subjects in these studies had non-stroke shoulder pain etiologies (Lathia et al., 2009; Vas et al, 2008).

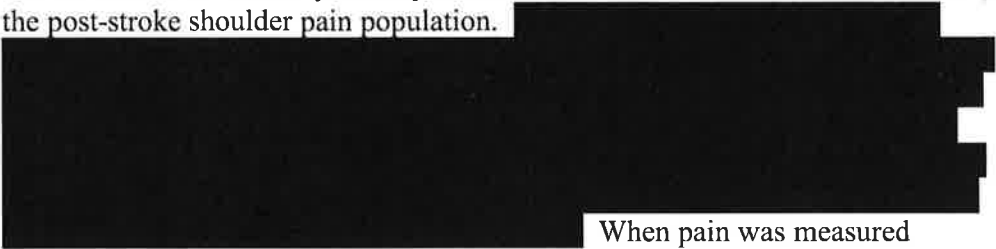
2.2.3 Electrical stimulation is a promising treatment for post-stroke shoulder pain

Electrical stimulation applied to intact lower motor neurons can activate paralyzed muscles (Sheffler and Chae, 2007; Moe and Post, 1962). One goal of using electrical stimulation in the hemiplegic arm is to relieve post-stroke shoulder pain. In the past 20 years, a series of clinical studies using either skin surface or percutaneous technology has evaluated electrical stimulation in the post-stroke shoulder. The results are summarized below.

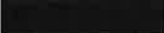
Surface electrical stimulation

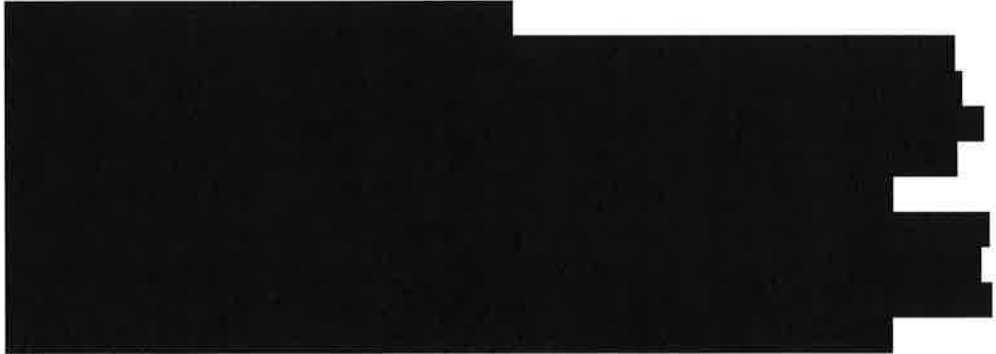
Surface electrical stimulation uses skin surface electrodes applied to the shoulder to deliver stimulation from an external stimulator. Baker and Parker published the first results from a randomized controlled trial of surface electrical stimulation for the treatment of post-stroke shoulder pain (Baker and Parker, 1986). The authors found a treatment effect for subluxation but inconclusive results regarding pain relief. The investigators of a later study hoped to obtain more conclusive results than Baker and Parker by enrolling a larger population of 120 and following the subjects for two years (Chantraine et al., 1999). Pain was noted as present or absent at rest during passive motion and during active motion. Subjects were also asked to rate their pain using a visual analogue scale (VAS). For a subject to be classified as having no pain, all four variables had to be negative. A significantly higher proportion of subjects receiving electrical stimulation had no pain at 3, 6, 12, and 24 months compared to the control group (80.7% vs. 55.1%, $p < 0.01$). The treatment subjects also showed a greater reduction in subluxation and a significant improvement in the recovery of arm motion.

The results of four additional studies (Faghri et al., 1994; Leandri et al., 1990; Linn et al., 1999; Sonde et al., 1998) investigating surface electrical stimulation are summarized in a Cochrane review (Price and Pandyan, 2001). Although the authors found a significant improvement in pain-free range of motion (ROM) in the treatment groups, the data did not support a significant reduction in pain intensity or incidence. The authors concluded that larger randomized controlled studies would be necessary to fully examine the effects of electrical stimulation in the post-stroke shoulder pain population.



When pain was measured directly, using a VAS, electrical stimulation was found to be more effective in preventing pain than conventional therapy (Kobayashi et al., 1999).

The results regarding the efficacy of surface electrical stimulation as a treatment for post-stroke shoulder pain have been promising, leading to its recommendation by several recently published guidelines (Teasell et al., 2003; Bates et al., 2005). In addition, a literature review proposed that surface electrical stimulation combined with gentle clinician guided exercises should be considered the “best practice” for acute stroke survivors (Turner-Stokes and Jackson, 2002). However, several authors have noted that even with further evidence of the efficacy of surface electrical stimulation, it is unlikely that it will ever be the standard of care due to the discomfort caused by stimulation of cutaneous pain receptors, the potential for skin irritation under multiple surface electrodes, the need for skilled personnel to place the surface electrodes on a daily basis, and muscle fatigue that commonly occurs due to the high frequency of stimulation (Baker and Parker, 1986; Faghri et al., 1994; Baker et al., 1988). Baker and Parker noted that either an implantable or a percutaneous system would have to be developed before electrical stimulation could become the preferred treatment. For these reasons, researchers have turned their attention to the use of  electrical stimulation.





Percutaneous [REDACTED] electrical stimulation

Percutaneous [REDACTED] electrical stimulation for the treatment of post-stroke shoulder pain was first studied at Case Western Reserve University by Chae and associates. A case report of a chronic stroke patient suffering from shoulder subluxation and pain, who was unable to tolerate surface electrical stimulation, suggested initial clinical feasibility of percutaneous electrical stimulation (Chae et al., 2001). The authors then conducted a pilot study in which eight chronic stroke survivors received six weeks of percutaneous electrical stimulation [REDACTED]. Subjects experienced a significant improvement in subluxation and self-reported pain (Yu et al., 2001a). This case series was duplicated in the Netherlands with similar reduction in shoulder pain (Renzenbrink and IJzerman, 2004); however, the study also demonstrated significant improvement in pain related quality of life based on the pain domain of the Medical Outcomes Study Short Form (SF-36).

The authors then conducted a double-blind crossover trial to determine whether sensation associated with percutaneous [REDACTED] electrical stimulation is less painful than sensation associated with surface electrical stimulation (Yu et al., 2001b). Subjects rated the pain of each treatment modality using a VAS and the Pain Rating Index of the McGill Pain Questionnaire (Melzack, 1975). The median scores on the VAS and the Pain Rating Index were lower for percutaneous electrical stimulation than for surface electrical stimulation ($p=0.007$ and $p=0.018$, respectively), indicating less pain with percutaneous electrical stimulation. In addition, nine out of ten subjects stated that they would prefer to receive percutaneous electrical stimulation over surface electrical stimulation.

Yu, Chae, and associates then went on to enroll 61 subjects into a single-blinded randomized controlled study to assess the effect of percutaneous [REDACTED] stimulation on shoulder pain and a variety of secondary endpoints (Yu et al., 2004; Chae et al., 2005). Treatment subjects received 6 hours of stimulation per day for 6 weeks while control subjects received a cuff type sling. Subjects were asked to rate their worst shoulder pain in the last week on an 11 point scale (Brief Pain Inventory short form, question 3) (Cleeland and Ryan, 1994) at various times throughout the 12 month follow-up. The group receiving electrical stimulation showed a significantly higher success rate (as measured by a minimum 2-point

reduction on the scale) than the control group (84% vs. 31%, $p=.001$ at the end of treatment). The authors concluded that percutaneous [REDACTED] electrical stimulation is safe and effective in reducing shoulder pain.

The need for a long-term therapy solution for post-stroke shoulder pain in a subset of stroke survivors is supported by a post-hoc analysis of the above study results (Chae et al., 2007). A logistic regression analysis of the study results was conducted post hoc to identify predictors of treatment success. The factor most predictive of treatment success was time from stroke onset. Specifically, subjects treated earlier (35.4 ± 16.4 weeks) post-stroke experienced a significant reduction in shoulder pain at the end of treatment and pain relief was maintained through 12-months post-treatment. Subjects treated later since their onset of stroke (211.4 ± 191.3 weeks) also achieved significant pain reduction at the end of treatment, but this pain reduction for these subjects dissipated with time after the therapy was turned off. [REDACTED]

[REDACTED] This post-hoc analysis concluded that future trials should consider investigating a permanently implanted device to treat the large prevalent stroke population that falls into the later group.

We are proposing a 2-stage therapy solution for this large prevalent stroke population in whom pain returns after treatment with a temporary system. The SPR Implant System will be offered to all subjects who respond to the SPR Trial Stage stimulation but have a clinically significant return of pain within 6 months. This miniature, minimally invasive Implant System will enable stroke shoulder pain sufferers to receive long-term pain relief without the undesirable side effects of other long-term therapies, such as medications.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.4 Advantages of the SPR System over alternative Surface Electrical Stimulation therapies

The SPR System has significant advantages over alternative Surface Electrical Stimulation therapies.

Consistent targeted stimulation.

The SPR System leads are placed and anchored [REDACTED], ensuring consistent stimulation [REDACTED] across treatment sessions, leading to greater reliability of the therapy. Consistent stimulation of the motor points ensures neurostimulation therapy is delivered to the affected area. Consistency is not ensured with surface stimulation, as electrodes must be placed for each therapy session, and could be placed in varying locations each time.

Reduced patient and clinician training.

Leads are placed only once by skilled personnel during the initial lead placement. Skilled personnel and intense patient training are not needed to ensure proper placement of leads for each subsequent treatment session, as is the case with the placement of surface electrodes.

Reduced stimulation-induced pain.

[REDACTED] electrical stimulation is less painful and better tolerated than surface electrical stimulation (Yu, et al., 2001). It is critical to the success of the therapy and overall patient compliance to be able to deliver the stimulation therapy in a comfortable and tolerable way.

Reduced [REDACTED] fatigue.

[REDACTED] electrical stimulation can be delivered at a lower stimulation frequency, which is associated with reduced muscle fatigue. Higher stimulation frequencies are used with surface electrical stimulation systems to minimize stimulation-induced cutaneous pain. It is important to minimize the potential for muscle fatigue in post-stroke patients so that they can still participate in the rehabilitation therapies for motor recovery.

Long-term pain relief.

The SPR Implant Stage uses the implantable SPR System, which enables patients to treat their pain symptoms if and when they return. This offers a long-term solution to shoulder pain that is within the patient's control. In addition, some individuals may have long-term pain relief following the short-term Smartpatch therapy.

[REDACTED]

[REDACTED]

[REDACTED]

2.6 Summary

[REDACTED]

The results obtained thus far suggest that [REDACTED] stimulation has the potential to be a safe and effective treatment option for post-stroke shoulder pain, but an approach using fewer leads and the option for a fully implantable system is needed to ensure ease of implementation and long-term effectiveness. The pilot study will be conducted by the sponsor, SPR Therapeutics, to gather preliminary safety, efficacy, and technical performance data on the SPR System. [REDACTED]

[REDACTED]

3.0 INVESTIGATIONAL DEVICE DESCRIPTION

3.1 Overview

The SPR System is a 2-stage neurostimulation device that applies electrical stimulation therapy [REDACTED] for the treatment of post-stroke shoulder pain. In the first stage (the SPR Trial Stage), [REDACTED] Trial stimulation is delivered for three weeks (following a 3-week off period for evaluation of sham stimulation) using an external stimulator (the Smartpatch Stimulator). If clinically meaningful pain reduction is achieved (at least at 2-point reduction on the Brief Pain Inventory Short Form Question #3) during the SPR Trial Stage but pain returns within 6 months and is sustained for two consecutive weeks, the subject progresses to receive an Implantable Pulse Generator (IPG) and Implantable [REDACTED] lead for long-term therapy (the SPR Implant Stage).

The SPR System consists of a Trial System and an Implant System, which are described in further detail below.

3.1.1 SPR Trial System (i.e., Smartpatch System) Components

The SPR Trial System consists of a:

- Percutaneous [REDACTED] Lead and Introducer (called the Smartpatch Lead and Introducer);
- A miniature programmable body-worn external stimulator and associated components known as the Smartpatch PNS System (comprised of a Smartpatch Stimulator, Smartpatch Pad, Smartpatch Cable supplied in two lengths, Smartpatch Test Cable, Smartpatch Test Needles, Smartpatch Lead Connector, Smartpatch Lead Connector Tape, and bandages).
- The Checkpoint® Test Stimulator and Test Cable (not shown in Figure 2) may be used by the Clinician to place the Lead



Figure 2. SPR Trial System

3.1.1.1 Smartpatch Lead

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.1.1.2 Smartpatch Lead Connector, Torque Wrench, and Lead Connector Tapes

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.1.1.3 Smartpatch Stimulator [REDACTED] and Smartpatch Pad ([REDACTED])

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.1.1.4 Smartpatch Cable [REDACTED]

[REDACTED]

[REDACTED]

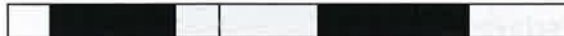
3.1.1.5 Checkpoint® Test Stimulator [REDACTED] and Checkpoint Test Cable [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

3.1.1.6 Smartpatch Test Cable

[REDACTED]

[REDACTED]

3.1.1.7 Smartpatch Test Needle

[REDACTED]



3.1.1.8 Accessories

[Redacted text block]

3.1.2 SPR Implant System Components

[Redacted text block]

- [Redacted text block]



3.1.2.1 Implantable Pulse Generator (IPG)

[Redacted text block]

[Redacted text block]

[Redacted text block]



3.1.2.2 Implantable Lead

[Redacted text block]

[Redacted text block]

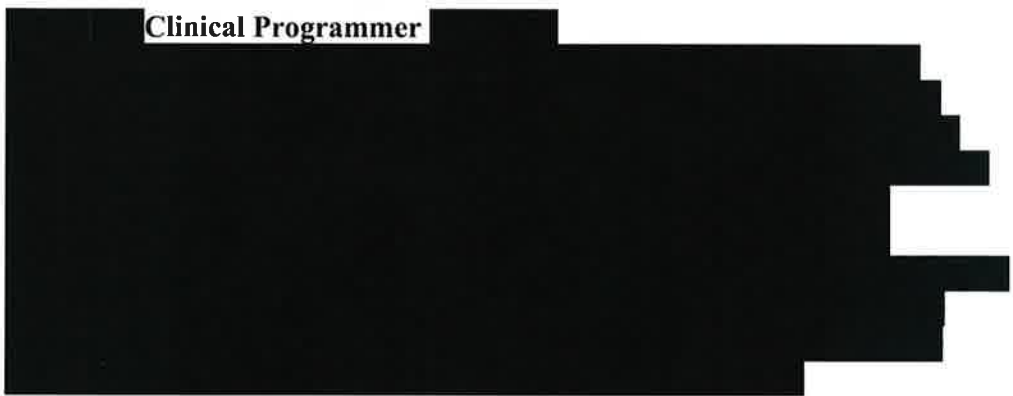
[Redacted text block]

[Redacted text block]

[Redacted text block]



Clinical Programmer



[REDACTED] IPG Remote [REDACTED], Charger [REDACTED] and IPG Shut-Off
Magnet [REDACTED]

IPG Remote

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

IPG Charger

[REDACTED]



IPG Shut-off Magnet



Introducer Tool



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Checkpoint Test Stimulator [REDACTED]
[REDACTED]
[REDACTED]

Modified IPG Remote



4.0 STUDY DESIGN

4.1 Overview

This study is a prospective non-randomized multicenter case series pilot study to gather preliminary data on the safety, clinical efficacy, and performance of the SPR System for the treatment of post-stroke shoulder pain.

Subjects with chronic (≥ 6 months) post-stroke shoulder pain rated as ≥ 4 on the Brief Pain Inventory pain intensity question #3 (BPI3) will receive the first stage of the SPR System. The SPR System is a two-staged neurostimulation therapy which delivers stimulation [REDACTED]. The first stage (SPR Trial Stage) uses a temporary [REDACTED] lead placed percutaneously in [REDACTED] and connected to a body-worn external stimulator (the Smartpatch Stimulator). Subjects meeting the specified success criteria at the conclusion of the SPR Trial Stage who then experience a return of pain within 6 months that is sustained for two consecutive weeks will be consented and screened for eligibility for the second stage (SPR Implant Stage). A “return of pain” is defined as: 1) an increase in pain by at least 2 points compared to the end

of Trial Stage (Visit 5) pain score; and 2) BPI Question #3 score of at least 4 (both criteria must be met for at least 2 weeks). The SPR Implant Stage uses an Implantable Pulse Generator (IPG) and Implantable [REDACTED] Lead.

Subjects will be permitted to continue use of non-opioid analgesic medications throughout the study; however, dosages of these medications will be controlled during the study. Subjects will be permitted to reduce or maintain their dosage of non-opioid analgesic medications, however, they will be asked to not increase their dosage of these medications above their baseline dosage during the week prior to each study visit and scheduled telephone call (and during the Trial Stage follow-up period). Subjects will not be permitted to use opioid analgesic medications (except in the week immediately following the implant stage surgery as needed to control post-surgical pain), or other treatment methods, including slings or other stabilization devices/methods, Botox or steroid injections to the affected shoulder area, etc, during study participation. For this study, Tramadol (Ultram, Ultram ER, or Ultracet) will be considered an opioid medication, and thus, not permitted during study participation. Subjects who require concurrent physical or occupational therapy for shoulder pain will be excluded.

Subjects will use the Smartpatch System for 6-weeks during the Trial Stage. To evaluate the placebo effect, the first 3-weeks of the SPR Trial Stage consist of a sham period in which the SPR Trial Stage device (i.e., the Smartpatch System) is placed, but stimulation is not delivered. Subjects are told that stimulation during lead placement may feel different than stimulation therapy. [REDACTED]

[REDACTED] Subjects will be blinded to the fact that stimulation is not being delivered. Following the sham period, stimulation will be delivered, and subjects will receive stimulation for a total of 6 hours each day for 3 weeks. Subjects will be queried for pain intensity on a weekly basis during the SPR Trial Stage using the BPI Short Form Question #3 (BPI3), and subjects will be instructed to focus on their shoulder pain when answering the BPI. Pain intensity at the end of the sham period will be compared to baseline pain intensity score to evaluate the placebo effect. At the conclusion of the SPR Trial Stage, subjects achieving at least a 2-point reduction on the BPI3 will receive monthly follow-up calls for up to six months in order to determine eligibility to advance to the SPR Implant Stage. During the Implant Stage, subjects will receive the fully implantable SPR Implant Stage system and be followed for three years.

All primary and secondary endpoints will be assessed at baseline and again at the completion of the sham period and the SPR Trial Stage. In addition, primary endpoints will be evaluated at all phone calls during the Trials Stage follow-up period and at all follow-up intervals during the SPR Implant Stage (3-weeks, 6-weeks, 12-weeks, 6-months, 9-months, and 12-months post IPG Stim ON). In addition, long-term follow-up will be conducted on an annual basis at 24-Months and 36-Months IPG Stim On.

Primary efficacy of the Trial Stage therapy will be determined at the end of the Trial Stage. Primary efficacy of the Implant Stage will be determined at the 12-week post-IPG Stim On follow-up visit. A subject will be considered a Trial Stage Success if he/she achieves at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the end of the Trial Stage (Visit 5) relative to end of the placebo period or baseline (Visit 4 or Visit 1), whichever is lower OR reports a BPI3 score of zero at the end of the Trial Stage.

A subject will be considered an Implant Stage success if he/she achieves at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the 12-week post-IPG stim on visit (Visit 10) relative to end of the placebo period or baseline (Visit 4 or Visit 1), whichever is lower OR reports a BPI3 score of zero at the 12-week post-IPG stim on visit.

All Implant Stage subjects will continue to be evaluated through the 36-month IPG Stim ON follow-up interval to determine the safety profile of the SPR Implant System and to evaluate the effect of dosage on treatment effect. Adverse events will be assessed at all follow-up visits.

4.2 Study Population

4.2.1 Selection Criteria

Subjects will be screened for eligibility from the available pool of candidates with post-stroke shoulder pain seen by the Investigator. The specific inclusion and exclusion criteria are listed in **Table 2** below. The total number of subjects and sites we are requesting for this study are listed immediately following the Inclusion/Exclusion Criteria and are presented in **Table 3**.

Table 2. Inclusion/Exclusion Criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> At least 21 years old ≥6 months after the stroke that caused shoulder pain Subject failed or did not tolerate at least two conservative therapies for a total period of at least 6 months since the onset of post-stroke shoulder pain. Shoulder pain as indicated by a score of ≥4 on the Brief Pain Inventory (BPI3) Upper extremity hemiplegia (No shoulder abduction, shoulder abduction in synergy or if 	<ul style="list-style-type: none"> Evidence of joint or overlying skin infection of the affected limb Taking any opioid medication (or Tramadol) for shoulder pain OR for any other chronic pain condition Intra-articular or sub-acromial steroid injections or botulinum toxin injections to the affected shoulder in the previous 12 weeks History of arrhythmia with hemodynamic instability, such as ventricular tachycardia, supraventricular tachycardia and rapid ventricular response atrial fibrillation OR valvular heart disease including artificial valves

<p>isolated movement is present, shoulder abduction $\leq 4/5$ on Medical Research Council (MRC) scale)</p> <ul style="list-style-type: none"> • Cognitive ability to fulfill study requirements based upon a score of ≥ 24 on the Mini Mental Status Exam (MMSE) • Ability to appropriately rank pain on a Numeric Rating Scale (based upon the Investigator's determination of the subject's ability to rank pain) • Availability of a reliable adult who can check the skin and assist the subject with the study protocol • Able and willing to take part in study <p>ADDITIONAL CRITERION FOR THE IMPLANT STAGE</p> <p>In addition to continuing to meet the above inclusion criteria (with the necessary pain score already having been confirmed at a Trial Stage Follow-up Call), subjects must:</p> <ul style="list-style-type: none"> • Be a Trial Stage Success AND • Have a clinically significant return of pain as defined by an increase in BPI3 score of at least 2 points (compared against the BPI3 score at Visit 5) resulting in a BPI 3 score of at least 4 within 6 months of the end of the Trial Stage that is sustained for at least two consecutive weeks. 	<ul style="list-style-type: none"> • Evidence of non-stroke related shoulder pathology with continuing symptoms (such as pathology related to a traumatic injury, tumor, or infection) • Bleeding disorder OR INR >3.0 for those on warfarin • Unable, per the prescribing physician, to stop antiplatelet medications [e.g., aspirin, clopidogrel (Plavix)] and/or anticoagulants for at least 7 days prior to SPR implantation. • Receiving outpatient physical or occupational therapy for shoulder pain • History of recurrent skin infections • Compromised immune system based upon medical history (i.e., HIV/AIDS, actively taking or recently completed immunosuppressive therapies such as chemotherapy or radiation of the head/neck, congenital immunodeficiency, or any other cause for compromised immune system documented in the medical history) • Medical instability that may interfere with ability to participate in a clinical trial as determined by the Principal Investigator • Severely impaired communication skills (receptive or expressive) as determined by the Principal Investigator • Confounding conditions such as ipsilateral upper limb lower motor neuron lesion, Parkinson's Disease, SCI, traumatic brain injury, MS, or complex regional pain syndrome • Uncontrolled seizures (>1 per month for 6 months) • An implanted electronic device • Allergy to skin surface electrodes and/or medical-grade adhesive tapes. • Allergy to local anesthetic agents such as lidocaine or previous reaction to Monitored Anesthesia Care (MAC) • Pregnant • Prisoners, minors, legally incompetent people, unconscious patients, house staff, or students
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We are requesting the following number of subjects and sites for our Pilot Study (Table 3).

Table 3. Subject and Site Totals Requested for Pilot Study

Description	Number of Subjects/Sites
-------------	--------------------------

Total Number of Subjects enrolled for eligibility (evaluation of minimum pain score on BPI3 inclusion criterion; INR testing in selected individuals, and pregnancy test)	Approximately 90
Total Number of Subjects undergoing SPR Trial Stage (Smartpatch System)	Up to 45
Total Number of Subjects with SPR Implant Stage (implantation of IPG and Implantable Lead)	Approximately 18
Number of Pilot Stage Investigational Sites	Up to 5 sites

4.2.2 Subject Disposition

Subject disposition in this study will be characterized as described in **Table 4** below.

Table 4. Subject Disposition Categories (continued on following page)

Disposition Category	Description
Screened Subjects	All subjects who are screened for potential study participation will be listed on a screening log. Those subjects who are excluded will be listed along with their reason for exclusion. Screened subjects include those individuals that were screened from record searches as well as those that came to the clinic, signed a consent form, and underwent further screening for eligibility.
Screen Failures (2 Levels)	Any subject who signs an Informed Consent and does not receive a SPR Trial Stage System will be dispositioned as a screen failure as follows: Level 1: Subjects who do not meet the pain intensity criteria (≥ 4 on the baseline BPI3). Level 2: Subjects who do not meet the criteria for the INR score or pregnancy test. [REDACTED]
Enrolled	Subjects who sign a consent form AND meet all eligibility criteria will be assigned a study ID and will be considered “enrolled” at that time. Any subject who has a lead replaced will only be counted once against total study enrollment.
SPR Trial Stage Failure	Subjects who receive the SPR Trial Stage System but do not demonstrate at least a 2-point reduction on the BPI3 during the Trial Stage.
Withdrawn	Subjects who voluntarily withdraw their study participation or are lost to follow-up will be categorized as withdrawn.
Terminated	Subjects who are prematurely terminated from the study by the Investigator. Termination forms will capture the reason for study termination.
Completed	Subjects who are Trial Stage successes and do not report a clinically significant and sustained return of pain within 6 months of the Trial Stage. OR Subjects who complete both the SPR Trial Stage and the Implant Stage and complete all follow-ups through the 36-month visit.

4.2.2.1 Subject Disposition following infection of Percutaneous or Implantable Leads

Subjects with infections related to the implanted electrodes will be treated and dispositioned according to the severity of the infection and the SPR stage (Trial or Implant). In the Trial Stage, subjects who develop a mild infection will receive the appropriate medical treatment (such as administration of antibiotics or wound cleansing) and the Smartpatch Lead will remain in the shoulder. An infection is considered to be “mild” when: 1) it is a superficial infection that does not involve a fever 2) it can be treated with topical antibiotics and/or appropriate cleansing agents and 3) it does not place the subject at risk for a deep tissue infection. These subjects will continue in the study.

Subjects who develop a moderate or severe infection (i.e any infection beyond what is described as mild above) during the Trial Stage or any infection of the components (Implantable Lead or IPG) during the Implant Stage will have the SPR System removed. These subjects will be followed until resolution of the infection. Upon resolution, the subject will be terminated from the study.

4.3 Justification for the Study Design

This study is a prospective non-randomized multicenter case series pilot study.



4.3.1 Sample Size Justification

A power analysis was conducted prior to initiation of the study ([REDACTED]). During conduct of the study, the sponsor compiled the data from six clinical trials (including data collected thus far in the present trial) on the treatment of post-stroke shoulder pain using peripheral nerve stimulation therapy. Across these six trials, [REDACTED] subjects experienced a clinically significant reduction in pain intensity. A power analysis was completed to reflect this success rate (Section 4.3.1.2).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.3.2 Justification of Treatment Duration

Our study design includes a 6-week SPR Trial Stage with 3-weeks of Sham Stimulation and 3-weeks of Trial Stage Stimulation. Previous [REDACTED] studies (Chae et al, 2005, Yu et al, 2004) used 6-weeks of stimulation, however further analysis of this data showed that the majority of pain reduction for the treatment subjects occurred during the first three weeks of stimulation. We anticipate that 3-weeks of SPR Trial Stage stimulation will be sufficient to determine which subjects will benefit from long-term therapy with the SPR System. Similarly, we anticipate that 3-weeks of sham stimulation will be sufficient to give us an indication of whether subjects experience a placebo effect from having the SPR Trial Stage System present. [REDACTED]

[REDACTED]

If a subject reports pain relief during the SPR Trial Stage but experiences the specified return of pain, he or she will advance to the SPR Implant Stage. As described above, a post-hoc analysis of the previous randomized controlled trial on [REDACTED] stimulation (Chae et al, 2005), demonstrated that stroke survivors who are treated later after stroke onset responded to a 6-week stimulation therapy but had a return of pain once the therapy was concluded. However, some stroke survivors who are treated soon after stroke onset may experience benefit from a temporary therapy for at least 12-months. Therefore, we are proposing that pain must return in order to warrant a fully implantable system.

4.4 Study Endpoints

4.4.1 Primary Endpoints

4.4.1.1 Reduction in pain intensity (Brief Pain Inventory)

The primary endpoint of the study is reduction in pain intensity over the past week as measured using the 11-point numerical rating scale of the Brief Pain Inventory (BPI3). The BPI is a widely used and validated 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. Invited participants included academic centers, regulatory agencies, the National Institutes of Health, the US Veterans Administration, and industry representatives. In addition, the BPI has been used in many chronic pain studies, including those for post-stroke shoulder pain, which demonstrated a significant reduction in pain intensity as compared to a standard of care control (Chae et al., 2005; Yu et al., 2004).

All subjects will be evaluated for a reduction in their worst pain intensity in the previous week (BPI3) at several key study visits: (1) at the completion of the 3-week sham period (Visit 4) to evaluate the placebo effect; (2) at the completion of the 3-week SPR Trial Stage stimulation period (Visit 5) to determine if the subject has met the criteria to be a Trial Stage Success; (3) during the Trial Stage follow-up period to assess for Implant Stage eligibility, and (4) at 3-weeks (Visit 8), 6-weeks (Visit 9), 12-weeks (Visit 10), 6-months (Visit 11), 9-months (Visit 12), 12-months (Visit 13), 24-months (Visit 14), and 36 months (Visit 15) following

the initiation of IPG Stimulation to determine efficacy of the implantable system. The BPI will be administered with stimulation turned off (for at least one hour prior to the study visit) and subjects will be instructed to focus on their shoulder pain when responding to the questions presented in the BPI.

The proportion of subjects achieving success in each stage will be calculated. A 2-point reduction in pain intensity is considered to be the minimum clinically important difference (MCID) on a 0-10 pain numeric rating scale (Farrar et al., 2001). Primary efficacy of the Trial Stage therapy will be determined at the end of the Trial Stage. Primary efficacy of the Implant Stage will be determined at the 12-week post-IPG Stim On follow-up visit. A subject will be considered a Trial Stage Success if he/she achieves at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the end of the Trial Stage (Visit 5) relative to end of the placebo period or baseline (Visit 4 or Visit 1), whichever is lower OR reports a BPI3 score of zero at the end of the Trial Stage.

In addition, the average reduction in pain intensity across all subjects during each stage will be analyzed.

4.4.1.2 Safety

The primary safety endpoint is the occurrence and type of device related adverse events (AEs). All AEs that occur during the study will be documented. Specific details regarding any observed AE will be collected on an AE Form and will be followed to resolution. The severity of each Adverse Event will be collected as well as its relationship to the SPR System. Any necessary treatment or intervention required and the resolution status of the adverse event will also be documented. AEs will be tabulated and summarized at the conclusion of the study. Additional details on the monitoring and adjudication of AEs is described in Section 11 (Data Safety Monitoring Board).

4.4.2 Secondary Endpoints

Several secondary endpoints are being collected to gain a better understanding of what effect, if any, the SPR System may have on each measure. We intend to evaluate these instruments (described below) to determine their usefulness in our future larger pivotal study on the 2-stage implantable system.

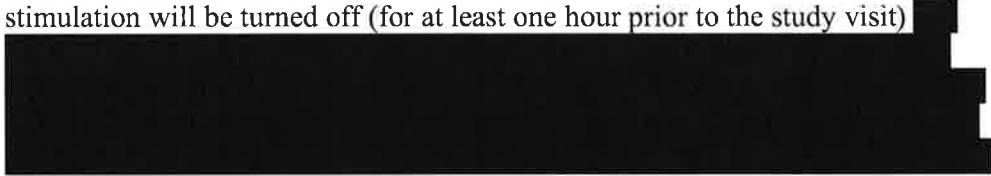
Similar to the primary endpoint, all secondary endpoints will be assessed when stimulation is off (for at least one hour prior to the study visit). Stimulation therapy is administered for 6 hours per day and thus, it is off for the majority of the day. All endpoints will be measured when stimulation is off (for at least one hour prior to the study visit) such that the overall impact of daily stimulation on the subjects' primary and secondary endpoints can be assessed, rather than the potential immediate effect of having stimulation on.

4.4.2.1 Reduction in Pain Interference

The degree to which shoulder pain interferes with daily activities will be assessed using Question 9 of the BPI (BPI9). This question asks the subject to rate the degree to which their pain has interfered with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life on a scale of 0 to 10, where 0 is “does not interfere” and 10 is “completely interferes”. The mean of these seven scores will be calculated to obtain the pain interference score. This pain interference endpoint will assist in assessing the impact of pain on activities of daily living and quality life. There is a strong relationship between the severity of post-stroke shoulder pain and BPI9 (Chae et al., 2007). Previous studies that evaluated the impact of neurostimulation therapy on post-stroke shoulder pain showed a significant reduction in the pain interference score when compared to controls (Chae et al., 2005; Yu et al., 2004). Similarly, we anticipate observing an improvement in pain interference in our study.

4.4.2.2 Pain-free passive range of motion (ROM)

Pain will also be assessed using the pain-free shoulder external rotation ROM assessment. Following stroke, the shoulder often demonstrates a decreased range of motion (Fugl-Meyer, 1980). This decrease in ROM is associated with shoulder pain (Bohannon et al., 1986). In order to measure the pain-free passive ROM, stimulation will be turned off (for at least one hour prior to the study visit)



Assessing the pain-free passive ROM is common in both clinical research and clinical practice as an objective measurement of pain (Chantraine et al., 1999; Faghri et al., 1994; Chae et al., 2005; Renzenbrink and IJzerman, 2004). Results will be analyzed to determine what impact, if any, the SPR System has on pain-free passive ROM. We expect no worsening of the pain-free ROM and will review the results to determine the usefulness of this measure for our pivotal study on the implantable system.

4.4.2.3 Medical Outcomes Study Short Form (SF-36v2)

It is important to measure the health-related quality of life (HRQOL) in chronic pain studies, as pain is known to impact daily activities (Dworkin et al., 2005). The SF-36v2 (Ware and Sherbourne, 1992) will be administered throughout the study to assess the change in HRQOL between the pre- and post-treatment periods. The SF-36v2 is a generic health survey designed to assess basic physical functioning and emotional well-being regardless of the disease or treatment. The 36 items are grouped into eight domains: physical functioning, role limitations due to physical problems, social functioning, bodily pain, general mental health, role limitations due to emotional problems, vitality, and general health perceptions. The SF-36v2 is the most commonly used generic measure of HRQOL and has shown acceptable reliability and validity in stroke populations (Anderson et al., 1996; Dorman et al., 1998). Results of the SF-36v2 will be analyzed to determine the instrument’s ability to detect changes resulting from

SPR therapy [REDACTED]

[REDACTED] In particular, results will be evaluated to ensure that there is no worsening of HRQOL.

4.4.2.4 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). The Patient Global Impression of Change (PGIC) scale will be administered 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. We expect the majority of subjects to demonstrate a positive response by selecting one of the three positive answers: 1) minimally improved, 2) much improved, or 3) very much improved.

4.4.2.5 Beck Depression Inventory Second Edition (BDI-II)

Chronic pain has both sensory and emotional aspects, making it important to measure depression in pain treatment studies (Leavitt et al., 1978; McWilliams et al., 2003). [REDACTED] we will be using the Second Edition of the Beck Depression Inventory (Beck et al., 1961). The BDI-II contains 21 groups of four statements, each group describing a depressive symptom. The respondent is to select the statement that best describes the severity of the given symptom. The BDI-II is recommended by the IMMPACT panel to measure emotional functioning. It has been used extensively in chronic pain clinical trials and has strong evidence of reliability, stability, and validity (Segal et al., 2008; Harris et al., 2008). [REDACTED]

4.4.2.6 Device Performance and User Satisfaction

The performance of the SPR Implant System will be evaluated at all follow-up visits. [REDACTED]

A physical examination of the Implantable Lead site and of the IPG pocket site will be performed at each of the follow-up visits. Physical examination of the sites will be used to evaluate the subject for potential adverse events as well as stability of the lead and IPG.

[REDACTED] We will monitor subject charging patterns and evaluate ease of use. [REDACTED]

Sponsor-developed satisfaction surveys will be administered to both the subjects and the clinicians to determine the overall satisfaction with the therapy and the technology. The results of the surveys will validate the study design and technology. The SPR System Subject Satisfaction Surveys will be administered to determine the overall subject satisfaction with the therapy and the usability of the SPR System. The SPR Trial Stage Subject Satisfaction Survey will be administered at the conclusion of the Trial Stage and the SPR Implant Stage Subject Satisfaction Survey will be administered at the 12-week and 12-month IPG Stim ON follow-up visits. In addition, two sponsor-developed Clinician Satisfaction Surveys will be administered. One survey will be administered to the Principal Investigator (the Physiatrist) and includes questions pertaining to both the SPR Trial and Implant Stages. The second survey will be given to the Investigator implanting the device (the surgeon) and includes questions related to the SPR Implant Stage procedure and the SPR therapy. [REDACTED]

[REDACTED]

These sponsor-generated surveys are being piloted during this study. [REDACTED]

[REDACTED]

4.4.2.7 Economic Impact of Shoulder Pain

At baseline, subjects will be asked to document pain medication, doctor visits, supplies (such as slings), related treatments (such as physical therapy for pain or psychotherapy for depression), need for caregivers, time spent in skilled nursing facilities, and lost work due to their shoulder pain. Subjects will be asked to recall this data for the 6-months prior to study enrollment. This raw data will be gathered from the subject. The Sponsor will then assign national average costs to each treatment used to determine the overall economic impact of shoulder pain.

Subjects will be permitted to complete this survey at home. The survey will not be monitored during routine monitoring visits and missing data will be not queried as is it anticipated that subjects may not be able to provide all the information requested.

4.4.2.8 Quantitative Sensory Testing (QST)

Quantitative Sensory Testing (QST) may be performed in order to determine if specific demographic, clinical, anatomic, physiologic, and psychological factors will categorize subgroups of participants according to their response to percutaneous IM PNS. The objective of the QST testing is to determine when a subject can first feel a sensation and when the sensation becomes painful.

The QST testing is optional and all elements of the QST may not be completed if the testing is found to take an excessive amount of time or if the subject is, for any reason, unable or unwilling to complete all of the testing. Subjects will be informed that there is a potential for skin irritation immediately following this testing.

QST testing will be performed at Visits 1,4,5, pre-6, 9, 11, and 13 and will consist of the following elements:

[REDACTED]

All measures described below, with the exception of the Conditioned Pain Modulation (CPM) protocol described below, will be obtained at three skin test sites:

[REDACTED]

The stimulation sites for the CPM are described in the section for “measures of central pain modulation,” below.

General QST testing information: Testing will be conducted in a quiet setting and subjects will be seated in a comfortable reclining chair. Subjects will be given a brief introductory session of the QST procedures. The introductory session will allow the subject to experience the range of stimuli to be presented and to familiarize themselves with the instructions for each test procedure.

Subjects will be instructed that they can stop the procedures at any time for any reason without penalty. All stimuli (with the exception of the cold water bath) will be presented with hand-held devices that can quickly be removed from the test site by the experimenter, or from which the subject can withdraw from the stimulus without constraint. All procedures to be used in this study, have been used in numerous published studies in a variety of subject groups and, for most

tests, involve threshold-level pain sensations induced by brief presentations of noxious stimuli.

Test administration will occur in the order that the tests are described below and will take approximately 2.5 hours to complete. Each type of test will be conducted at all 3 skin test sites before moving to the next test procedure, so that stimulation at one body site will occur for a brief period of time followed by at least 3 minutes of “rest” before stimulation occurs at that site again. Longer breaks of stimulation will be utilized between the series of temporal summation trials and between the temporal summation protocol and CPM protocol, to insure that any pain from the procedure has resolved.

QST Instruments and Equipment:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Measures of Tactile/Mechanical Sensory Function:

■ *Tactile/touch detection thresholds* will be measured using four series of stimulus presentations of the graded TouchTest monofilaments (North Coast Medical) at each test site. [REDACTED]

- *Vibration detection thresholds* will be measured using the VSA component of the TSA-II device (Medoc, Ltd.). [REDACTED]

[REDACTED] Three trials will be performed at each test site.

Measures of mechanical pain sensory function:

■ *Pin prick pain threshold* will be measured using graded force mechanical probes with small probe tips (MRC Systems). [REDACTED]

■ *Pressure pain threshold* will be measured using a manual pressure algometer. [REDACTED]

Measures of thermal detection and thermal pain function: The TSA-II (Medoc, Ltd.) will be used to deliver thermal stimuli via a thermal probe [REDACTED]

[REDACTED] The probe will be held lightly against the skin as the temperature increases (for warm detection and hot pain thresholds) or decreases (for cool detection and cold pain thresholds) from a baseline temperature that approximately matches the neutral skin surface temperature (32°C). Subjects will be instructed to verbally respond when the desired sensation is reached. [REDACTED]

[REDACTED] Each type of sensation threshold (cool detection, warm detection, cold pain, hot pain) will be measured three times at each test site.

Measures of temporal summation of pain: Repeated administration of brief noxious stimuli will be performed to investigate temporal summation of pain (increased sensation of pain with repetitive stimulation at the same stimulus intensity). Two types of stimuli will be used for this: mechanical stimuli (using the pin prick stimulators) and thermal stimuli (using the TSA-II device).

[REDACTED]

Measure of conditioned pain modulation: The conditioned pain modulation (CPM) protocol consists of two types of stimuli: the test stimulus (which will be a brief thermal stimulus set at a mild to moderately painful temperature, [REDACTED] and the conditioning stimulus (a cold water bath set at a temperature [REDACTED]). The test stimulus will be presented to the volar forearm at the beginning of the CPM protocol and the subject will be asked to rate the pain intensity of the sensation produced by this stimulus. The subject will then submerge his/her foot into the cold water bath [REDACTED]. The same thermal stimulus will then be presented to [REDACTED] forearm again and the subject will be asked to rate the pain intensity of the stimulus. One trial of CPM will be performed.

4.4.2.9 Reduction in arm impairment and improvement in Activities of Daily Living using the Stroke Upper Limb Capacity Scale (SULCS)

The Stroke Upper Limb Capacity Scale (SULCS) will be used to test the hypothesis that a reduction in post-stroke shoulder pain will be associated with reduction in arm impairment and improvement in activities of daily living (ADLs) compared to baseline. [Roorda, 1992] The SULCS will be performed at Visits 1,4,5, pre-6, 9, 11 and 13.

The SULCS is a validated upper limb capacity scale which includes tasks directly related to activities of daily living individuals experience in their home environment. The SULCS consists of 10 items, with each item having a possible score of 0 or 1: 3 items for arm capacity without active hand capacity; 4 items for

arm capacity and basic hand capacity; and, 3 items for complex hand capacity. The SULCS takes approximately 10-15 minutes to complete.

4.5 Study Procedures

Detailed Schedules of Procedures are presented in **Table 5** SPR Trial Stage Schedule of Procedures and **Table 6** SPR Implant Stage Schedule of Procedures below. In addition, specific details regarding each study visit are described in Sections 4.5.1 through 4.5.3 below. In addition, Study Visit Windows are detailed in Section 4.6 below.

Table 5. Schedule of Procedures- SPR TRIAL STAGE

Assessment / Procedure	BASELINE		SHAM PERIOD				SHAM/ TRIAL	TRIAL STIMULATION			FOLLOW-UP	
	Visit 1 (Baseline)	Visit 2 (Trial Stage Procedure)	Visit 3 (48-hour safety check)	Telephone Call #1 (1-week Sham)	Telephone Call #2 (2-weeks Sham)	Visit 4 (End of sham period/ Turn Trial Stim ON)	Telephone Call #3 (1-week Trial Stim ON)	Telephone Call #4 (2-weeks Trial Stim ON)	Visit 5 (End of Trial Stim/End of Trial Stage)	Visit Post-5 (Trial Stage 1-week Follow-up visit)	Telephone Calls #a-z (Trial Stage Follow-up calls)*	
Informed consent obtained	X – Trial Stage											
Verify General Inclusion/Exclusion	X											
BPI Short Form	X			X-Q3 only	X-Q3 only	X	X-Q3 only	X-Q3 only	X		X-Q3 only	
MMSE	X											
INR measured, pregnancy test	As needed											
Pain-free passive ROM	X					X			X			
PGIC						X			X			
BDI-II	X					X			X			
SF-36v2	X					X			X			
Economic Survey	X											
SULCS	X					X			X			
QST testing	X-optional					X-optional			X-optional			
Trial System Procedure		X										
Stimulation turned ON/Programming		X-Initiate sham				X-Terminate sham						
Inspect Percutaneous Exit Site			X			X			X			
Subject Trial Stage Satisfaction Survey Administered									X			
Assess Adverse Events		X	X	X	X	X	X	X	X	X	X	
Assess Subject Compliance						X			X			
Remove Trial Lead									X			
Assess effectiveness of Blinding				X	X	X						

Table 6. Schedule of Procedures- SPR IMPLANT STAGE

		SPR IMPLANT STAGE											
Assessment / Procedure	Visit Pre-6 (Implant Stage Eligibility)	Visit 6 (Implant Stage Procedure)	Visit 7 (1-week Post-Implant/ Turn IPG Stim ON)	Telephone Call #5 (1-week IPG Stim ON)	Telephone Call #6 (2-weeks IPG STIM ON)	Visit 8 (3-weeks IPG Stim ON)	Visit 9 (6-weeks IPG Stim ON)	Visit 10 (12-weeks IPG Stim ON)	Visit 11 (6-Months IPG Stim ON)	Visit 12 (9-Months IPG Stim ON)	Visit 13 (12-Months IPG Stim ON)	Visit 14 (24-Months Post-IPG Stim ON)	Visit 15 (36-Months IPG Stim ON)
Informed consent obtained	X – Implant Stage												
Verify General Inclusion/Exclusion	X												
BPI Short Form													
MMSE	X												
INR, pregnancy tests	As needed												
Implant Stage Procedure		X											
INR													
Pregnancy Test													
BPI Short Form				X-Q3 only	X-Q3 only	X	X	X	X	X	X	X	X
Pain-Free PROM						X		X	X	X	X	X	X
PGIC						X		X	X	X	X		
BDI-II						X		X	X	X	X		
SF-36v2						X		X	X	X	X		
SULCS	X						X		X		X		
QST	X-optional						X-optional		X-optional		X-optional		
Turn ON IPG Stim			X										
IPG Programming		X	X-As needed			X-as needed	X-as needed	X-adjust dosage	X-adjust dosage	X-adjust dosage	X-adjust dosage	X-As needed	X-As needed
Inspect Implant Sites			X			X	X	X	X	X	X	X	X
Subject Implant Stage Satisfaction Survey Administered								X			X		
Assess Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess Subject Compliance						X	X	X	X	X	X	X	X
Assess Recharge History						X	X	X	X	X	X	X	X

4.5.1 Baseline (Visit 1)

Potential study participants will be screened for eligibility from a pool of candidates with post-stroke shoulder pain and recorded in the Subject Screening Log. Patients meeting all general eligibility criteria will be asked if they are interested in participating in the study. The Informed Consent Form will be reviewed with the potential subject to ensure that the risks and benefits of study participation are fully understood. The Informed Consent for this study consists of two documents: the Trial Stage Consent Form and the Implant Stage Consent Form. Prior to any data collection, subjects who agree to participate in the study must sign the Trial Stage Informed Consent Form and will be asked to read the Implant Stage Consent Form such that the risks of participating in both phases of the study are presented to the subject. The Trial Stage Informed Consent Form may be signed up to 30 days prior to the SPR Trial Stage procedure. Prior to the Implant Stage procedure, the study participants who qualify to progress onto the Implant Stage (and agree to continue to the Implant Stage) will be asked to review and sign the Implant Stage Consent Form such that the risks of participating in that phase of the study are clearly understood.

Subjects will then be screened for their cognitive ability to participate in the study and complete the required surveys. The Mini Mental Status Exam (MMSE) will be administered to determine the subject's cognitive ability to participate in the study. The MMSE has been validated as a cognitive function survey instrument and has been widely used in stroke patients. Subjects must score ≥ 24 on the MMSE in order to qualify.

The Investigator will also determine their ability to rank pain based on interactions during the screening process or prior medical interaction with the subject.

Subjects will then be given the Brief Pain Inventory Short Form to determine their baseline degree of pain. Subjects will be instructed to focus on their shoulder pain when answering the BPI and must rate their worst pain in the last week as ≥ 4 on the BPI3 numeric rating scale to qualify for the study.

As a safety precaution to prevent potential excessive bleeding, subjects on warfarin will have blood drawn to confirm an INR of <3.0 . If the INR is not below 3.0, 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 SPR Trial Stage procedure. In addition, a pregnancy test will be conducted in females of reproductive potential.

Once a subject has met all eligibility criteria, the Subject ID will be assigned.

During this visit, subjects will also be assessed for Pain-Free Range of Motion, complete the SF-36v2, complete the BDI-II, and be provided with an Economic

Impact Survey for completion at home. The SULCS and the QST testing (optional) will also be completed at this visit for subjects enrolled following the integration of these tests into the protocol.

Information regarding baseline pain medications (including type, dosage, and frequency) will be collected from the subject and/or their caregiver during this visit. Medications will be categorized as to whether they are used to treat shoulder pain or other types of pain. Subjects will be asked to control these pain medications. They will be instructed that dosages of pain medications should be maintained or can be decreased from their baseline dosage during the week prior to each study visit and phone call for the duration of their study participation. Thus, subjects will be asked to not increase their medication dosages above their baseline dosage during the week prior to each study visit and phone call for the duration of their study participation. The 1-week period was selected because the primary endpoint, BPI pain intensity, asks subjects to recall their worst pain in the past week.

Due to the frequency of visits during the Trial Stage, this medication protocol asks subjects to maintain or decrease their dosages throughout the duration of the Trial Stage. For pain medications that are taken on an as needed basis (e.g. "PRN"), subjects will be queried at baseline for their highest "as needed dose". Future "as needed" dosages during the week prior to the study visits and phone calls should not exceed this dosage.

If pain medication for breakthrough shoulder pain or other types of pain is required beyond their baseline dosage, this will be documented and analyzed in accordance with Sections 6.1 and 6.2.

4.5.2 SPR Trial Stage

4.5.2.1 SPR Trial Stage Procedure/Start of sham period (Visit 2)

Following the baseline visit, subjects will return to the clinic for the SPR Trial Stage Procedure. During the SPR Trial Stage procedure, a Smartpatch Lead will be placed. At the conclusion of this visit, the sham period will begin for each subject.

To determine a suitable location for placement of the Smartpatch Lead,

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Prior to leaving the clinic, subjects and their caregivers will be instructed on the proper care of the percutaneous lead exit site. To initiate the 3-week sham period, the Smartpatch Stimulator and Smartpatch Pad will be connected to the Smartpatch Lead (via the Smartpatch Lead Connector). The Investigator will then program the stimulator to deliver sham stimulation (i.e., no stimulation), which is further described in the SPR Clinician Manual. [REDACTED]

[REDACTED] The subject will be instructed on how to turn stimulation on/off and how to connect and disconnect the Smartpatch Stimulator, Smartpatch Pad, Smartpatch Cable, Lead Connector Tapes, and adhesive bandages. The subjects will be instructed to use the Smartpatch Stimulator for a total of 6 hours each day.

[REDACTED] Subjects will be blinded to this sham period

[REDACTED] Subjects will also be instructed that they may or may not feel some of the stimulation levels.

Data regarding the specific details of the SPR Trial Stage procedure will be collected during this visit. In addition, the SPR Trial Stage procedure may be video taped for educational and training purposes. Subject faces will not appear in the video and each subject will sign a separate video consent (if applicable at the Investigational Site) if they agree to be video taped.

A detailed description of the SPR Trial Stage procedure and programming instructions, including instructions for Sham Programming Mode, for the Smartpatch System is provided in the Clinician Manual.

4.5.2.2 48-hour Post-Lead Placement Safety Check (Visit 3)

In order to mitigate the potential risk of infection, subjects will return to the clinic for a check of the Lead exit site within 48 hours of the SPR Trial Stage procedure. The exit site will be examined for any signs of early infection. If any signs of infection are observed, the subject will be provided with appropriate treatment, including possible removal of the percutaneous lead. Please refer to details regarding the proper disposition of subjects who develop an infection in Section 4.2.2.1.

4.5.2.3 1-week Sham (Telephone Call #1)

Subjects will be contacted via telephone 1-week following the start of the sham period. During this telephone call, subjects will be queried for pain intensity (BPI3), adverse events, and medication usage. Subjects will also be asked to select between two statements related to the effectiveness of subject blinding. These statements are further described in Section 4.5.2.5.

4.5.2.4 2-week Sham (Telephone Call #2)

Subjects will be contacted via telephone again 2-weeks following the start of the sham period to query for pain intensity (BPI3), adverse events, and medication usage. Subjects will also be asked to select between two statements related to the effectiveness of subject blinding. These statements are further described in Section 4.5.2.5.

4.5.2.5 End of Sham Period/Turn Trial Stimulation ON (Visit 4)

Three weeks following the SPR Trial Stage procedure (Visit 2) and at the conclusion of the sham period, subjects will return to the clinic for evaluation. Primary and secondary endpoints will be evaluated including the BPI, Pain Free Passive Range of Motion, SF-36v2, the Patient Global Impression of Change scale, and the BDI-II. The SULCS, and QST testing (optional) will be administered to subjects for which baseline SULCS and QST data are available, specifically, subjects who were enrolled after the incorporation of these tests into the protocol. The skin will be checked for evidence of infection. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records. At the conclusion of the visit, the effectiveness of subject blinding will be evaluated by asking subjects to select the statement that best describes their experience in the past week: 1) I think stimulation was on some or all of the time during my daily stimulation sessions; 2) I think stimulation was off during my daily stimulation sessions. In order to be classified as blinded, a subject must respond that stimulation was on at least once during the sham period. A subject will be classified as not blinded if they respond that stimulation was off three times during the sham period (indicating that they did not believe stimulation was on at any time).

During this visit, the Investigator will [REDACTED] to begin the 3-week trial stimulation regimen. Stimulation parameters will initially be programmed based [REDACTED] identified during SPR Trial Stage procedure. If necessary, adjustments will be made to these parameters, [REDACTED]. Subjects will then be sent home with stimulation turned on and will be reminded of the proper use of the Smartpatch stimulator and continued care of the Lead exit site.

4.5.2.6 1-week Trial Stim ON (Telephone Call #3)

Subjects will be contacted via telephone 1-week following the start of the trial stimulation. During this telephone call, subjects will be queried for pain intensity (BPI3), adverse events, and medication usage.

4.5.2.7 2-week Trial Stim ON (Telephone Call #4)

Subjects will be contacted via telephone again 2-weeks after the start of trial stimulation to query for pain intensity (BPI3), adverse events, and medication usage.

4.5.2.8 3-Week Trial Stim ON/End of Trial Stage (Visit 5)

At the end of the 3-week trial stimulation regimen (6-week total SPR Trial Stage), subjects will return for evaluation of primary and secondary endpoints including the BPI, Pain Free Passive Range of Motion, SF-36v2, BDI-II, and the Patient Global Impression of Change scale. The SULCS and QST testing (optional) will

be administered to subjects for which baseline SULCS and QST data are available. Questions regarding general satisfaction and device performance will be asked in the SPR Trial Stage Subject Satisfaction Survey. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records.

The Lead will then be removed during this visit [REDACTED]. The Investigator will perform a visual inspection of the removed Lead. If results of the visual inspection are suggestive of a broken Lead or retained fragment, the Investigators will determine what is medically required to further evaluate and treat the retained fragment.

If the subject achieves a satisfactory response to trial stimulation by demonstrating at least a 2-point reduction in the BPI3 from the End of the Trial Stage stimulation (Visit 5) compared to the End of Sham (Visit 4), the subject will be considered a Trial Stage success. The subject will be followed for up to 6 months to assess the return of pain as described in Section 4.5.2.10. Subjects who demonstrated a negative placebo effect (as evidenced by a worsening of the BPI during the Sham stimulation period) will be compared against Baseline (rather than End of Sham) to assess if they are Trial Stage Successes. Subjects who do not achieve at least a 2-point reduction in BPI will be considered SPR Trial Stage failures.

4.5.2.9 Trial Stage Follow-up Visit (Visit Post-5)

All subjects will be asked to return to the clinic for a final visit one week following removal of the Lead. During the 1-week follow-up visit, the percutaneous site will be inspected to ensure that there are no signs of infection or other adverse events. SPR Trial Stage failure subjects, and those who choose not to continue, will then be terminated from the study. The Trial Stage Follow-up Calls will be scheduled for all subjects continuing in the protocol. Any AEs noted at this visit will be followed to resolution prior to subject termination.

4.5.2.10 Trial Stage Follow-up Calls (Telephone Calls #a-z)

Subjects meeting the specified success criteria at Visit 5 will receive monthly phone calls from the study staff until the specified return of pain is reported (for up to 6 months). A return of pain is an increase in the BPI Question #3 score (worst pain in the last week) by at least 2 points and equaling at least a 4 on the scale. In addition to querying the subject about his/her pain, the study staff will also assess for adverse events.

Once a return of pain is reported, an additional call will be scheduled for one week later. During this call, if the subject still reports the specified return of pain, the eligibility visit for the Implant Stage will be scheduled (Visit Pre-6). If the subject no longer reports the specified return of pain, additional phone calls may be conducted until a return of pain is sustained for at least two weeks. At any

time during the six months following Visit 5, Trial Stage Follow-up Calls may be conducted to assess pain. In addition to the monthly calls, the subject may call the study staff at any time within 6 months of Visit 5 to report a return of pain and be assessed for potential eligibility for the Implant Stage. Such a call will be assigned the next call identifier (a through z) and conducted identical to the monthly calls.

If a subject does not report the specified return of pain within 6 months, he/she will be dispositioned as “complete” (see Table 4) and terminated from the study.

During the Trial Stage Follow-up Period, subjects will be permitted to continue use of non-opioid analgesic medications; however, dosages of these medications will be controlled as they are during the Trial Stage and Implant Stage. Subjects will be permitted to reduce or maintain their dosage of non-opioid analgesic medications; however, they will be asked to not increase their dosage of these medications above their baseline dosage at any time (as the phone calls to determine return of pain can occur at any time during the six month period). Subjects will not be permitted to take opioid analgesic medications; receive injections to the affected limb; receive physical or occupational therapy; or, use slings or other stabilization devices/methods during this period.

4.5.2.11 Provision for lead replacement during Trial Stage

During the Trial Stage, it is possible that the Smartpatch Lead may migrate from the intended target location or may become fully dislodged. In the event that the Lead migrates from the intended location significantly ([REDACTED] or if the lead becomes fully dislodged (i.e. comes out completely), it is possible that the Investigator may elect to place another trial stage lead. This decision will be at the discretion of the 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 Trial Stage lead placement would apply a second time, 2) the Investigator’s belief that the intended target location is healthy enough to place another lead, and 3) the amount of time remaining in the trial stage.

Subjects who initially required an INR test prior to the first Trial Stage lead placement, will have the test repeated within 48 hours of a second Trial Stage lead placement, as necessary.

If a second Trial Stage lead is placed, subjects will be asked to return to the clinic 48 hours after the lead placement for inspection of the lead exit site. In addition, stimulation therapy will not be turned on for at least one week [REDACTED]. Subjects will then continue with the sham or treatment stage as is appropriate under the protocol.

The risks associated with any additional Trial Stage lead placement procedures are the same as the risks detailed for the initial procedure and are described in Section 8.2 of this protocol. However, subjects will have an additional exposure to this risk.

4.5.3 SPR Implant Stage

4.5.3.1 Implant Stage Eligibility (Visit Pre-6)

After a sustained return of pain has been identified, the subject will report to the clinic for Visit Pre-6. First, the study staff will verify that the subject meets all general inclusion and exclusion criteria (with the necessary pain score already having been confirmed at a Trial Stage Follow-up Call). Subjects meeting all general eligibility criteria will be asked if they are interested in participating in the Implant Stage of the study. The Implant Stage Informed Consent Form will be reviewed with the subject to ensure that the risks and benefits of study participation in the Implant Stage are fully understood. The Implant Stage Informed Consent Form may be signed up to 30 days prior to the Implant Stage procedure.

Subjects will then be screened for their cognitive ability to participate in the study and complete the required surveys. The Mini-Mental Status Exam (MMSE) will be administered to determine the subject's continued cognitive ability to participate in the study.

During this visit, the SULCS, and QST testing (optional) will also be administered to subjects for which baseline SULCS and QST data are available.

As a safety precaution to prevent potential excessive bleeding, subjects on warfarin will have blood drawn to confirm an INR of <3.0 . If the INR is not below 3.0, 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 Implant Stage procedure. In addition, a pregnancy test will be conducted in females of reproductive potential.

If the subject is determined to be eligible, the Implant Stage procedure (Visit 6) will be scheduled.

4.5.3.2 SPR Implant Stage Procedure (Visit 6)

Subjects will be asked to comply with any specific preoperative or post-operative instructions (including prescribing of post-surgical pain management analgesics in the week immediately following surgery) or testing that are the standard practice for the implanting surgeon (Investigator). This may require a separate visit to the institution in order to obtain the necessary standard pre-operative tests for clearance to obtain anesthesia.

Prior to the procedure, the IPG will be programmed [REDACTED]. The settings are based upon the optimal [REDACTED] that was identified in the SPR Trial Stage.

The SPR Implant Stage procedure will be performed in an operating room, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Subjects will be given standard post-operative instructions including restricting physical activity for the first week after the implant procedure and may be prescribed opioid or non-opioid analgesics, as needed, for the management of post-surgical pain during the week immediately following the Implant Stage surgery.

As with the SPR Trial Stage, the SPR Implant Stage procedure may be videotaped for training and educational purposes.

A detailed description of the SPR Implant Stage procedure and IPG programming is provided in the Clinician Manual.

4.5.3.3 1-week Post-Implant/ Turn IPG Stim On (Visit 7)

One week following the SPR Implant Stage Procedure, subjects will be asked to return to the clinic for a physical inspection of the IPG pocket and Implantable Lead sites and to turn stimulation on.

The Clinician will [REDACTED] program the IPG for the subject. Stimulation parameters will be based [REDACTED] but will be adjusted as needed. Subjects will be instructed to use the SPR System for a total of 6 hours per day.

The subject will be provided with the IPG Remote and instructed on how to turn the stimulation on/off, how to adjust the intensity [REDACTED] how to charge the IPG and details on the care and maintenance of the IPG Remote and the other accessories to the SPR Implant System. [REDACTED]

Adverse events will be assessed and a standard post-operative evaluation will be conducted.

4.5.3.4 1-week IPG Stim On (Telephone Call #5)

One week after IPG stimulation has been turned on, subjects will be contacted via telephone to query for pain intensity (BPI3), adverse events, medication usage, and details regarding the IPG charging pattern.

4.5.3.5 2-Week IPG Stim On (Telephone Call#6)

Subjects will be contacted via telephone again 2 weeks after the start of IPG stimulation to query for pain intensity (BPI3), adverse events, medication usage, and details regarding the IPG charging pattern.

4.5.3.6 3-Week IPG Stim On (Visit 8)

Following 3 weeks of IPG stimulation, subjects will return for evaluation of primary and secondary endpoints including the BPI, Pain Free Passive Range of Motion, SF-36v2, BDI-II, and the Patient Global Impression of Change scale. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records.

4.5.3.7 6-Week IPG Stim On (Visit 9)

Following 6 weeks of IPG stimulation, subjects will return for evaluation of the primary endpoint (the BPI) and to perform a safety check of the IPG and Implantable IM Lead sites and [REDACTED] of the SPR System. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records. Subjects will also be queried for medication usage and adverse events.

During this visit, the SULCS, and QST testing (optional) will be administered to subjects for which baseline SULCS and QST data are available.

4.5.3.8 12-Week IPG Stim On (Visit 10)

Following 12 weeks of IPG stimulation, subjects will return for evaluation of primary and secondary endpoints including the BPI, Pain Free Passive Range of Motion, SF-36v2, the BDI-II, the Patient Global Impression of Change scale, and a Subject Satisfaction Survey. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records. The 12-week visit will serve as the primary efficacy analysis for the SPR System.

At the end of the visit, the number of daily hours of stimulation will be modified according to the pain relief reported by the subject:

- If the subject's BPI Question #3 score is ≤ 2 , the dosage (number of hours of stimulation per day) will be reduced from 6 hours to 4 hours.
- If the subject's BPI Question #3 score is greater than 2 but at least two points less than the baseline score (i.e., still reporting clinically significant pain relief), the dosage will remain at 6 hours per day.

- If the subject's BPI Question #3 score is not 2 points less than it was at baseline, the dosage will remain at 6 hours and the system will be checked for any technical problems.

4.5.3.9 6-Month IPG Stim On (Visit 11)

Following 6 months of IPG stimulation, subjects will return for evaluation of primary and secondary endpoints including the BPI, Pain Free Passive Range of Motion, SF-36v2, BDI-II, and the Patient Global Impression of Change scale. The SULCS and QST testing (optional) will be administered to subjects for which baseline SULCS and QST data are available. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records.

At the end of the visit, the number of daily hours of stimulation will be modified according to the pain relief reported by the subject:

- If the subject's BPI Question #3 score is ≤ 2 , the dosage [REDACTED]
- If the subject's BPI Question #3 score is greater than 2 but at least two points less than the baseline score (i.e., still reporting clinically significant pain relief), the dosage [REDACTED]
- If the subject's BPI Question #3 score is not 2 points less than it was at baseline, the dosage will [REDACTED]

4.5.3.10 9-Month IPG Stim ON (Visit 12)

Following 9 months of IPG stimulation, subjects will return for evaluation of primary and secondary endpoints including the BPI, Pain Free Passive Range of Motion, SF-36v2, BDI-II, and the Patient Global Impression of Change scale. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records.

At the end of the visit, the number of daily hours of stimulation will be modified according to the pain relief reported by the subject:

- If the subject's BPI Question #3 score is ≤ 2 , the dosage [REDACTED]
- If the subject's BPI Question #3 score is greater than 2 but at least two points less than the baseline score (i.e., still reporting clinically significant pain relief), the dosage [REDACTED]
- If the subject's BPI Question #3 score is not 2 points less than it was at baseline, the dosage [REDACTED]

4.5.3.11 12-Month IPG Stim ON (Visit 13)

Following 12 months of IPG stimulation, subjects will return for evaluation of primary and secondary endpoints including the BPI, Pain Free Passive Range of Motion, SF-36v2, BDI-II, the Patient Global Impression of Change scale, and a Subject Satisfaction Survey. The SULCS and QST testing (optional) will be administered to subjects for which baseline SULCS and QST data are available. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records.

At the end of the visit, the number of daily hours of stimulation will be modified according to the pain relief reported by the subject:

- If the subject's BPI Question #3 score is ≤ 2 , the dosage [REDACTED]
- If the subject's BPI Question #3 score is greater than 2 but at least two points less than the baseline score (i.e., still reporting clinically significant pain relief), the dosage [REDACTED]
- If the subject's BPI Question #3 score is not 2 points less than it was at baseline, the dosage [REDACTED]

4.5.3.12 Annual Long-Term Follow-Up Visits (Visits 14 and 15)

Subjects will return to the clinic annually for long-term follow-up visits at 24-Months and 36-Months IPG Stim ON. During these visits, the BPI and Patient Global Impression of Change scale will be administered. Subjects will also be queried for medication usage and adverse events. To assess participant compliance with the stimulation regimen, [REDACTED] will be recorded in the subject records.

4.5.3.13 Unscheduled Visits

Subjects may need to return to the clinic for an unscheduled visit if they experience a technical issue with their SPR System or adverse event which requires further evaluation by the clinical study staff.

4.5.3.14 Explant Follow-Up Visit

Subjects requiring an explant of the SPR Implant Stage System (either the IPG, Implantable IM Lead, or both) will be required to return to the clinic for a 1-week follow-up visit after the explant procedure.

4.5.3.15 Revision Surgery Visit(s) -If Applicable

As noted in the risk section of this protocol, it is possible that subjects may require a revision surgery due to 1) migration of the implantable components resulting in loss of efficacy or subject discomfort, 2) failure of the implantable components, 3) rejection of the implantable components, 4) removal of the system due to a medical condition that requires MRI scanning, or 5) any other medical condition which necessitates removal of the system. If a revision surgery is necessary, the risks and any potential benefits of undergoing an additional surgical procedure will be discussed with the subject. Revision surgeries carry the same risks as the original implantation procedure and any additional subject specific risks will be discussed with the subject prior to any revision surgery. Additional visits to the clinic will also be necessary if a revision procedure is performed.

4.6 Study Visit Windows

The acceptable windows for each visit and telephone call are listed in **Table 7**.

Table 7. Study Visit and Telephone Call Windows

Visit Number	Visit Name	Window
N/A	Trial Stage Consent Form	
1	Baseline Visit	
2	Trial Stage Procedure/Start of Sham	
3	48-hour Safety Check	
	Telephone Call #1	
	Telephone Call #2	
4	End of Sham/Turn ON Trial Stim	
	Telephone Call #3	
	Telephone Call #4	
5	3-weeks Trial Stim ON/End of Trial Stage	
Post-5	Trial Stage Follow-up Visit	
	Telephone Calls #a-z	
Pre-6	Implant Stage Eligibility/Consent	
6	Implant Stage Procedure	

7	1-Week Post-Implant / Turn IPG Stim ON	
	Telephone Call #5	
	Telephone Call #6	
8	3-Weeks IPG Stim ON	
9	6-Weeks IPG Stim ON	
10	12-Weeks IPG Stim ON	
11	6-Month IPG Stim ON	
12	9-Month IPG Stim ON	
13	12-Month IPG Stim ON	
14	24-Month IPG Stim On	
15	36-Month IPG Stim On	

4.7 Study Duration

The duration of the study is expected to be up to 10 years. The study will be conducted at up to five sites enrolling a total of 45 SPR Trial Stage subjects to yield approximately 18 subjects in the SPR Implant Stage. Study enrollment of 45 SPR Trial Stage subjects is expected to take approximately 7 years, and subject participation for those who progress to the SPR Implant Stage can last approximately 3 years.

4.8 Early Termination

It is possible that this pilot study may be terminated prior to reaching 45 subjects participating in the SPR Trial Stage. Criteria for early termination of the study are detailed in Section 10.2.

4.9 Subject Compensation

Subject compensation for participation in the study is presented in **Table 8**.

Table 8. SPR Subject Compensation Schedule

Visit Description	Visit or Call Number	Amount
Baseline	Visit 1	
SPR Trial Stage Procedure/Start of Sham Period	Visit 2	
48-hour Post-Lead Placement Safety Check	Visit 3	
1-week Sham (Telephone Call #1)	Call #1	
2-week Sham (Telephone Call #2)	Call #2	
End of Sham Period/Turn Trial Stimulation ON	Visit 4	
1-week Trial Stim On (Telephone Call #3)	Call #3	
2-week Trial Stim On (Telephone Call #4)	Call #4	
3-Week Trial Stim On/End of Trial Stage	Visit 5	
Trial Stage Follow-up Visit	Visit Post-5	
Trial Stage Follow-up Calls	Calls #a-z	

Implant Stage Eligibility	Visit Pre-6	
Implant Stage Procedure	Visit 6	
1-week Implant Follow-Up/ Turn IPG Stim ON	Visit 7	
1-week IPG Stim On (Telephone Call #5)	Call #5	
2-Week IPG Stim On (Telephone Call#6)	Call #6	
3-Week IPG Stim On	Visit 8	
6-Week IPG Stim On	Visit 9	
12-Week IPG Stim On	Visit 10	
6-Month IPG Stim On	Visit 11	
9-Month IPG Stim On	Visit 12	
12-Month IPG Stim On	Visit 13	
24-Month IPG Stim On	Visit 14	
36-Month IPG Stim On	Visit 15	
Unscheduled Visit (if applicable)- subjects who are asked to return to the clinic for an unscheduled visit will be compensated \$40.	No Visit Number	
TOTAL		

In addition to compensation for the study visits, when necessary, it is possible that transportation may be arranged for by the site on behalf of the study participant and covered by the study budget. Alternatively, subjects who are able to drive will receive reimbursement for mileage at the standard federal reimbursement rate.

5.0 DATA MANAGEMENT AND ANALYSIS

5.1 Data Collection

Baseline Case Report Forms (CRFs) will be completed for each subject who signs an informed consent. Subjects who sign an Informed Consent Form but do not receive a SPR Trial Stage System will not have any further data collected. The reason why the percutaneous lead was not placed will be documented in the subject's study file.

CRFs will be completed and maintained in a fashion that is consistent with accepted Good Clinical Practices used for Case Report Forms. 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 unless, as stated above, the subject signed an Informed Consent, but did not elect to proceed in the study. 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).

5.2 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 Health Insurance Portability and Accountability Act (HIPAA) regulations will be followed.

5.3 Data Processing

SPR Therapeutics, LLC, or its designated Contract Research Organization (CRO), will be responsible for database creation, double 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.

5.4 Data Analysis

All primary and secondary endpoint data will be analyzed and reported. This study is a non-randomized case series involving up to 45 SPR Trial Stage and approximately 18 SPR Implant Stage subjects.

5.4.1 Primary Efficacy Endpoint Analysis

Within subject analyses of the primary endpoint, the BPI3, are performed for each subject throughout the study. First, the BPI3 is collected and analyzed at the end of the sham period during the SPR Trial Stage, to evaluate the placebo effect. Second, the BPI3 is collected at the conclusion of the SPR Trial Stage to determine the proportion of subjects who experienced clinically significant pain relief during the Trial Stage (i.e., Trial Stage Success proportion). Third, the BPI3 is collected during the Trial Stage Follow-up period to assess the return of pain and determine if a subject is eligible to advance to the SPR Implant Stage. Finally, the BPI3 is collected and analyzed during the SPR Implant Stage to determine the success of the SPR Implant System for the individual.

A subject will be considered a Trial Stage Success if he/she achieves at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the end of the Trial Stage (Visit 5) relative to end

of the placebo period or baseline (Visit 4 or Visit 1), whichever is lower OR reports a BPI3 score of zero at the end of the Trial Stage.

A subject will be considered an Implant Stage success if he/she achieves at least a 2-point reduction in post-stroke shoulder pain intensity score in the BPI Pain Intensity Question #3 (BPI3) at the 12-week post-IPG stim on visit (Visit 10) relative to end of the placebo period or baseline (Visit 4 or Visit 1), whichever is lower OR reports a BPI3 score of zero at the 12-week post-IPG stim on visit.

A description of each analysis is presented below and details regarding the statistical methods are presented in Section 6.

5.4.1.1 Determination of Placebo Effect During SPR Trial Stage

For each subject, a within subject analysis will be performed to evaluate if a placebo effect occurred during the sham stimulation period. The BPI3 score collected at the End of the sham period (Visit 4) will be compared to the BPI3 score collected at Baseline (Visit 1).

If

P_0 = BPI pain score at Baseline

P_1 = BPI pain score at End of Sham

Then, a positive placebo effect is present in any subject who has a decrease in their BPI3 score from Baseline to the End of Sham:

$$P_1 < P_0$$

Alternatively, a negative placebo effect is present in any subject who has an increase in their BPI3 score from Baseline to the End of Sham:

$$P_1 > P_0$$

There is no placebo effect observed if a subject does not have a change in their BPI3 score from Baseline to the End of Sham:

$$P_1 = P_0$$

5.4.1.2 Determination of SPR Trial Stage Success

To determine if a subject is a Trial Stage Success, the BPI3 will be collected at the conclusion of the 6-week SPR Trial Stage. For each subject, the BPI3 score reported at the End of Trial Stim (Visit 5) will be compared to the BPI3 score reported at the End of Sham (Visit 4).

If

P_0 =BPI pain score at Baseline

P_1 =BPI pain score at End of Sham

P_2 =BPI pain score at End of Trial Stim

Then, subjects who demonstrate a positive placebo effect (or no placebo effect) will be considered SPR Trial Stage successes if they demonstrate a 2-point or greater decrease in their BPI3 score from the End of Sham to the End of Trial Stim:

$$P_1 - P_2 \geq 2$$

If the BPI3 score at End of Sham (P_1) is less than 2 (e.g. the value is 1 or 0), then BPI3 at the End of Trial Stage (P_2) must equal 0 to be considered a Trial Stage Success.

Alternatively, subjects who demonstrate a negative placebo effect (as evidenced by an increase in the BPI3 score during the sham period) will be compared to Baseline (Visit 1), rather than End of Sham. It is critical to compare to the Baseline BPI3 score for these subjects, to ensure that they have achieved pain reduction as a result of the stimulation therapy and not as a result of a placebo effect.

For these subjects, they will be considered SPR Trial Stage successes if they demonstrate a 2-point or greater decrease in their BPI3 score from Baseline to the End of Trial Stim:

$$P_0 - P_2 \geq 2$$

5.4.1.3 Determination of return of pain after Trial Stage

To determine if a subject is eligible to advance from the SPR Trial Stage to the SPR Implant Stage, the BPI3 will be collected at least monthly for up to 6 months following Visit 5 (the end of Trial Stage stimulation) for those subjects who are Trial Stage successes. For each subject, the BPI3 score reported at the phone call will be compared to the BPI3 score reported at the End of Trial Stim (Visit 5).

If

P_2 =BPI pain score at End of Trial Stim

P_3 =BPI pain score at phone call

Then, subjects will be eligible to be screened for the Implant Stage if they demonstrate a sustained 2-point or greater increase in their BPI3 score from End of Trial Stim and their new BPI3 score is at least a 4:

$$P_3 - P_2 \geq 2 \text{ (sustained for two consecutive weeks)}$$

$$P_3 \geq 4 \text{ (sustained for two consecutive weeks)}$$

5.4.1.4 Determination of SPR Implant Stage Success

Implant Stage subject success will be determined by comparing their BPI3 score collected at 12-weeks IPG Stim ON (Visit 10) to the End of Sham BPI3 score (Visit 4).

If

P₀=BPI pain score at Baseline

P₁=BPI pain score at End of Sham

P₂=BPI pain score at End of Trial Stim

P₄=BPI pain score at 12-weeks IPG Stim ON

Then, subjects demonstrating a positive placebo effect (or no placebo effect) will be considered an Implant Stage success if they demonstrate a 2-point or greater decrease in their BPI3 score from End of Sham to 12-weeks of IPG stimulation therapy:

$$P_1 - P_4 \geq 2$$

As with the determination for pain relief in the SPR Trial Stage, subjects who demonstrate a negative placebo effect (increase in the BPI3 score after End of Sham) will have their BPI3 score at 12-weeks of IPG stimulation therapy (Visit 10) be compared to their score at Baseline (Visit 1).

For these subjects, they will be considered an Implant Stage success if they demonstrate a 2-point or greater decrease in their BPI3 score from Baseline to 12-weeks of IPG stimulation therapy:

$$P_0 - P_4 \geq 2$$

5.4.1.5 Summary of Pain Score Comparisons

Table 9 summarizes the comparisons that are necessary to determine whether or not a placebo effect is present in each subject, if a subject is a Trial Stage Success, if the subject is eligible to advance to the SPR Implant Stage, and if a subject is considered an Implant Stage success.

Table 9. Summary of Pain Score Comparisons

Baseline BPI3	End of Sham BPI3*	Result of Comparison of Sham vs. Baseline	Placebo Effect	End of Trial Stage BPI3*	Trial Stage Success Criteria	Criteria to be consented/ screened for the Implant Stage	12-weeks IPG Stim ON	Implant Stage Success Criteria
P ₀	P ₁	P ₁ < P ₀	Positive placebo effect	P ₂	P ₁ - P ₂ ≥ 2	P ₃ - P ₂ ≥ 2 P ₃ ≥ 4	P ₄	P ₁ - P ₄ ≥ 2
P ₀	P ₁	P ₁ = P ₀	No placebo	P ₂	P ₁ - P ₂ ≥ 2	P ₃ - P ₂ ≥ 2 P ₃ ≥ 4	P ₄	P ₁ - P ₄ ≥ 2

P_0	P_1	$P_1 > P_0$	Negative placebo effect	P_2	$P_0 - P_2 \geq 2$	$P_3 - P_2 \geq 2$ $P_3 \geq 4$	P_4	$P_0 - P_4 \geq 2$
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*If the BPI3 score at End of Sham (P_1) is less than 2 (e.g. the value is 1 or 0), then BPI3 at the End of Trial Stage (P_2) must equal 0 to be considered a Trial Stage success.

5.4.2 Primary Safety Analysis

All adverse events will be documented, reported, and categorized so that we may further understand the safety profile of this approach. The severity of each Adverse Event will be collected as well as its relationship to the SPR System. Any necessary treatment or intervention required and the resolution status of the adverse event will also be documented. Knowledge gained from this study will further refine consent forms and the risk benefit profile for future studies.

5.4.3 Secondary Endpoint Analysis

As with the primary endpoint, we will analyze what effect, if any, the treatment has on pain interference (BPI9), Pain Free Passive Range of Motion, SF-36v2, BDI-II, the Patient Global Impression of Change scale, the SULCS, and subject satisfaction. QST testing is optional and thus an analysis will be completed if sufficient data are gathered.

Pain interference (BPI9), Pain Free Passive Range of Motion, SF-36v2, and BDI-II, the SUCLS, and QST Testing are collected at the End of Trial Stage, 3-weeks, 12-weeks, 6-months, 9-months, and 12-months post IPG Stim ON. These secondary endpoints will be compared to the End of Sham. In addition, the pain interference (BPI9) is also collected at 6-weeks, 24-months and 36-months post IPG Stim ON and will be compared to End of Sham. As with the primary endpoints, subjects demonstrating a negative placebo effect for secondary endpoints will be compared to Baseline.

Results of the Patient Global Impression of Change scale and the subject satisfaction survey will be independently summarized to assess for a positive response indicating overall subject satisfaction with the system and therapy.

6.0 STATISTICAL METHODS

6.1 Planned Interim Analysis

6.1.1 Interim Safety Review (annual)


The Chairman of the DSMB (described further in Section 11) will review and adjudicate the accumulating safety data at least annually (once enough safety data have accumulated) to monitor for trends that would warrant modification or termination of the trial and will convene the DSMB if any concerns regarding the safety of the trial arise, such as a UADE.

We will continue enrollment if the safety profile is as expected. We may elect to close enrollment based upon the recommendations of our DSMB safety

evaluation or if we find that changes to the SPR System are necessary prior to enrolling additional subjects.

6.1.2 Interim Safety and Efficacy Analysis (all subjects)

Once all subjects who have advanced from the Trial Stage to the Implant Stage have completed the 12-week IPG Stim On evaluation (Visit 10), an interim analysis will be conducted by our DSMB to monitor safety and clinical efficacy. End of Trial Stage data (Visit 5) will be compared to data collected at the End of Sham (Visit 4) or baseline, where necessary. In addition, efficacy data collected at Visit 12 will be compared to data collected at the End of Sham (Visit 4) or baseline, where necessary.



In addition, similar analyses will be conducted once all subjects have completed the 6, 12, and 24 months IPG Stim On evaluations.

The following analyses will be conducted on the interim data for all subjects.

6.1.2.1 Placebo Effect

An analysis of the primary endpoint will be conducted using the data from the BPI Question 3 to evaluate the placebo effect in the overall study population. The proportion of successes at the End of Sham visit (Visit 4) will be compared to the proportion of successes at the End of Trial Stage in order to determine the pain intensity reduction during the sham period compared to 3-weeks of SPR Trial Stage stimulation. The Wilcoxon signed rank test will be used to assess the significance of the median change in BPI3.

6.1.2.2 SPR Trial Stage Success

Trial Stage success for each subject is the binary outcome pertaining to success (a 2-point or greater decrease in BPI3 during the Trial Stage or failure (a decrease of less than two points, no change in BPI3, or increase of BPI3 during the Trial Stage). BPI3 at the end of the Trial Stage (Visit 5) will be compared to BPI3 at the End of Sham (Visit 4) for subjects who demonstrate either no placebo or a positive placebo effect. For subjects in whom a negative placebo effect was observed, BPI3 results at Visit 5 will be compared against Baseline (Visit 1).

6.1.2.3 SPR Implant Stage Success

Implant Stage success for each subject is the binary outcome pertaining to success (a 2-point or greater decrease in BPI3) or failure (a decrease of less than two points, no change in BPI3, or increase of BPI3) during the Implant Stage of the study. This endpoint will be compared between 12-weeks IPG Stim ON (Visit

10) and the End of Sham (Visit 4) for subjects who demonstrate either no placebo or a positive placebo effect. For subjects in whom a negative placebo effect was observed, results will be compared against Baseline (Visit 1).

6.1.2.4 Overall study success

Overall study success is defined by the success rate across all subjects participating in each stage, and is expected to exceed the historically observed success rate [REDACTED] based upon previous and ongoing studies that demonstrated a [REDACTED] success rate among subjects treated with stimulation therapy (Yu et al., 2001a; Chae et al, 2005; Chae et al., 2013; Wilson et al., 2014; as well as the present study and an unpublished randomized controlled trial).

A test of significance will be carried out to test the null hypothesis that the success rate [REDACTED] or less versus the alternative that the true success rate exceeds [REDACTED]. In addition, a 95% confidence interval for the true success rate will be reported with the expectation that the lower limit of the interval will exceed [REDACTED]

All treatment failures, including any subjects who had an Implant Stage system removed due to an adverse event, will also be analyzed as part of this analysis.


Finally, a logistic regression will be reported, treating subject success as the binary outcome and baseline BPI as a possible explanatory variable. Other subject characteristics, such as time post-stroke, cortical vs. subcortical, right vs. left affected shoulder, and subluxation versus non-subluxation will be examined via a covariate analysis.

Secondary endpoints will be assessed using non-parametric tests. The Wilcoxon signed-rank test will be used to examine the difference of each endpoint for each subject. We will also investigate the mean improvement by reporting the results using a one-sample t-test.

This interim analysis will also include an examination of mean changes in the normalized dose of nonopioid medications using pain medication data collected at baseline from the subject (including type, dosage, frequency, and whether the medication is used to treat shoulder pain or other types of pain) compared against each subsequent visit. The analysis will be used to confirm that pain medication dosages did not increase for the week prior to each visit and call and during the Trial Stage follow-up period, in accordance with the study protocol. Although subjects will be asked to maintain pain medication dosages, an increase in dosage for breakthrough pain is permitted. For this pilot study, there is no limit on the number of pain medication uses for breakthrough shoulder pain or other types of pain. The number of uses of breakthrough medication will be analyzed for each subject. Further analysis of this data will be used to evaluate the need for limits on rescue medications for breakthrough pain during the future pivotal study on the implantable system.

6.2 Final Analysis

A final analysis will be conducted after all subjects have completed the study. This analysis will be on the 36-month IPG Stim ON follow-up visit. The analysis will be identical to the analysis on the 12-week IPG Stim ON data, with the exception that most secondary endpoints are not collected at the 36-month visit. In addition, an examination of mean changes in the normalized dose of nonopioid medications at 36-months will be performed as described in Section 6.1.2.4 above.



7.0 STUDY MONITORING AND DEVICE ACCOUNTABILITY PROCEDURES

7.1 Study Monitoring

7.1.1 Training

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

7.1.2 Routine Monitoring

Monitoring visits to each Investigational Site will be conducted following the enrollment of the first 2 subjects at the site and then periodically, as determined by the rate of subject enrollment, during the study. These visits are conducted 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.

The Investigational Site will maintain all source documentation in either paper or electronic format. SPR Therapeutics clinical monitors or their authorized representatives will be granted access to these source documents during each visit for verification against the CRFs. The site regulatory files will be reviewed during monitoring visits, as needed, to ensure that current amendments and approvals have been obtained.

The study records may also be subject to a quality assurance audit by SPR Therapeutics (or their authorized representatives), as well as inspection by appropriate regulatory authorities. Site personnel are required to be available

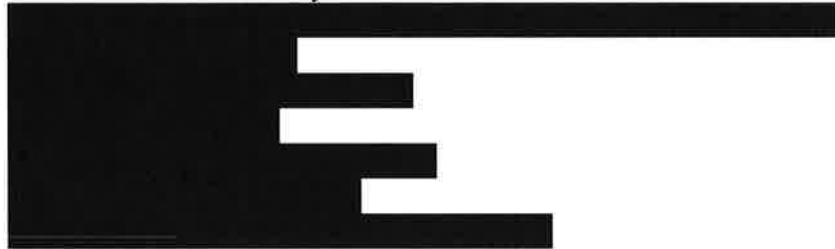
during the monitoring visits and audits and ensure that sufficient time is dedicated to this process.

7.2 Device Accountability

Device accountability will be maintained by the Investigational Site. The number of devices delivered to the site, clinically used, and returned by the Investigator will be registered. The Investigator is responsible for ensuring that all devices are maintained under controlled conditions with access limited to Investigational study team members. The monitor will reconcile device accountability during the monitoring visits, as needed. Any accountability discrepancies will be explained in writing by the Investigator.

7.3 Designation of Study Monitor

The monitor for this study will be:



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

7.4 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 SPR System. AEs will be classified as mild (event that causes mild discomfort or inconvenience and resolves without treatment), moderate (event that requires medical intervention or medication to treat), or severe (event that requires intervention to prevent permanent impairment or damage, an event that requires or prolongs hospitalization, or an event that is disabling, causing permanent damage, life threatening, or causing death). Any necessary treatment or intervention required and the resolution status of the adverse event will also be documented. Adverse Events will be followed to resolution.

An Adverse Device Effect (ADE) is a device-related Adverse Event. All adverse device effects are further categorized as anticipated or unanticipated. Any adverse device effects specified in the Risk Analysis of this Investigational Plan will be considered “anticipated”. All other adverse device effects 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.

Study Personnel will report any UADE by telephone and fax within 24 hours of learning of the event. The event is reported by telephone and a completed AE form will be faxed to SPR Therapeutics staff as indicated in **Table 10**. Follow-up information and the complete UADE report will be forwarded to SPR Therapeutics as the event continues and/or resolves.

During Investigator Training, the site will be provided with detailed instructions to report AEs and UADEs. Instructions will be in compliance with SPR Standard Operating Procedures for reporting adverse events in clinical studies. Sponsor contact information for reports of Unanticipated Adverse Device Events is provided in **Table 10**.

Table 10. Unanticipated Adverse Device Event Sponsor Contact Information

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

It is the responsibility of the Investigator to inform his Institutional Review Board (IRB) of any ADEs and UADEs as required by the IRB. In addition, some IRBs will require that AEs that are serious in nature, even if not device related, will be reported as well. SPR Therapeutics is responsible for furnishing the required information to the appropriate regulatory authorities.

8.0 RISK BENEFIT ANALYSIS

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

8.1 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:

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

In addition, this research may benefit future patients with post-stroke shoulder pain through knowledge gained or treatments developed through this research.

8.2 Known and Anticipated Risks

[REDACTED]

8.2.1 SPR Trial Stage Risks

The following risks are associated with the SPR System Trial Stage:

1) Risks associated with needle insertion for Smartpatch Lead placement

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2) Risk of skin irritation, infection, or inflammation at the Smartpatch Lead exit site

[REDACTED]

[REDACTED]

[REDACTED]

3) Risk of the Smartpatch Lead breaking beneath the skin

[REDACTED]

[REDACTED]

[REDACTED]

4) Risk of infection associated with retained Smartpatch Lead fragments

[REDACTED]

[REDACTED]

5) Risks associated with lead fragment removal

[REDACTED]

[REDACTED]

6) Risk of Lead Replacement due to Lead Migration or Lead Becoming Dislodged

[REDACTED]

[REDACTED]

7) Risk of skin irritation under the Smartpatch Pad, Smartpatch Lead Connector Tape, or bandages

[REDACTED]

[REDACTED]

8) Risk of mechanical or electrical failure of the Smartpatch Stimulator

[REDACTED]

[REDACTED]

9) Risks for pregnant women

[REDACTED]

[REDACTED]

10) Risk of discomfort due to electrical stimulation

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

11) Risks associated with Diathermy

[REDACTED]

[REDACTED]

12) Risks associated with MRI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

13) Risk of allergic reaction to local anesthetics and/or risk of accidental injection of local anesthetic into a vein

[REDACTED]

[REDACTED]

[REDACTED]

14) Risk associated with venipuncture (if applicable)

[REDACTED]

[REDACTED]

[REDACTED]

15) Risk of worsening of pain symptoms

[REDACTED]

[REDACTED]

8.2.2 SPR Implant Stage Risks

1) General Risks of Surgery and Anesthesia

[REDACTED]

[REDACTED]

[REDACTED]

2) **Risks of the SPR Implant Stage Procedure**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3) Risk associated with venipuncture (if applicable)

[REDACTED]

[REDACTED]

[REDACTED]

4) Risk of immunological rejection of the implanted components or materials

[REDACTED]

5) Risk of failure of the implanted components of the SPR System

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6) Risk of migration of the Implantable Lead or IPG

[REDACTED]

7) Risk of breakage of the Implantable Lead or a Lead fragment remaining in the body if the Lead is removed

[REDACTED]

[REDACTED]

[REDACTED]

8) Risks of Implantable Lead Fragment Removal

[REDACTED]

9) Risks during pregnancy

[REDACTED]

10) Risk of mechanical or electrical failure of the IPG Remote.

[REDACTED]

11) Risk of skin erosion over the Implantable Lead or IPG.

[REDACTED]

[REDACTED]

- 12) Risk of discomfort and/or pain associated with SPR Implant Stage stimulation.

[REDACTED]

- 13) Risk of skin burns or tissue heating near the IPG.

[REDACTED]

- 14) Risk of MRI

[REDACTED]

[REDACTED]

- 15) Risk of skin irritation associated with the use of the adhesive patches

[REDACTED]

- 16) Risk of deriving no benefit from the SPR Implant Stage System

[REDACTED]

17) Risk of worsening of the subject's pain symptoms

[REDACTED]

18) Risk of interference with the SPR System by external radiofrequency sources

[REDACTED]

19) Risk of injury or damage to implantable components

[REDACTED]

20) Risk of interference with medical monitoring equipment

[REDACTED]

21) Risks associated with long-term stimulation

[REDACTED]

8.3 Risk Analysis

All efforts are being made to mitigate each potential risk associated with the use of the SPR System for post-stroke shoulder pain. Despite efforts to reduce the risks associated with participation in this study, it is still possible that the risks noted above, and other additional unanticipated risks, may occur. Anticipated risks have been mitigated to reduce their frequency and severity; therefore the potential benefit of long-term pain relief for post-stroke shoulder pain outweighs the potential risks of participation in the study.

9.0 ETHICAL CONSIDERATIONS

9.1 Declaration of Helsinki

The study will be performed in accordance with the relevant parts of the International Conference of Harmonisation (ICH) Guidelines for Good Clinical Practices (GCPs), the Declaration of Helsinki, ISO 14155:2011 and the FDA regulations.

9.2 Institutional Review Boards

It is the responsibility of the Principal Investigator for each site 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.

9.3 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.

9.4 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 and 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.

10.0 STUDY ADMINISTRATION

10.1 Record Retention

By signing this study protocol, the Investigator agrees to retain study-related documents in a secure location to which access can only be gained if required. Following study completion, the following documents will be archived: the study regulatory files containing all Good Clinical Practice (GCP) documents, including signed Informed Consent forms, subject-related materials, and CRFs. The Investigator will be required to retain records for a period of 2 years after completion of the study, withdrawal of the IDE, or PMA approval, whichever is latest. The investigator must inform SPR Therapeutics if the location of the records changes or if there are any plans to destroy the records.

10.2 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 and IRBs will be notified in writing in the event of a study termination.

[REDACTED]

[REDACTED]

10.3 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. In addition, a study center may be terminated if the center has severe protocol violations without the necessary justification or with inadequate corrective actions.

[REDACTED]

10.4 Investigator Qualifications/Responsibilities and Investigator Training

To participate in this study, the Investigator must sign the Investigator Agreement which documents his/her responsibilities in the study.

Investigators participating in this study will require training on the clinical study protocol, investigational device, and device implantation and implementation. Education on these key elements is necessary to ensure suitable Investigator training and proficiency. These elements will be covered during an Investigator/Coordinator Training session. Training may be accomplished with other Investigators during a large group session or may be performed at a particular site. Regardless of the physical location and format of the training course, all of the specific elements of Investigator and Coordinator training will be addressed.

The Investigator/Coordinator Training must include the following elements; however the curriculum may be slightly modified as necessary:

[REDACTED]

[REDACTED]

In addition, Investigators and Coordinators will be required to participate in a Site Initiation Visit for their respective Investigational Site. A Site Initiation Visit will be conducted once the following has occurred:

- FDA approval of the IDE is obtained
- Site IRB approval has been obtained
- A signed Clinical Study Agreement has been executed with the institution
- All other site regulatory documents are on file at the sponsor and at the site

The Site Initiation Visit will involve a review of some of the materials covered at the Investigator/Coordinator training. In addition, more specific details will be covered. A Site Initiation Visit must include the following elements, however the curriculum may be slightly modified as necessary:

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

11.0 DATA SAFETY MONITORING BOARD (DSMB)

An independent Data Safety Monitoring Board (DSMB) will be assembled consisting of three clinical experts who have no affiliation with SPR Therapeutics and are not participating in the trial. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



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