Official Title:
A Randomized, Controlled, Multicenter Trial of Percutaneous Peripheral Nerve Stimulation (PNS) for the Treatment of Back Pain

NCT#: 04246281

Date: 4 April 2024

RESET

Clinical Trial

A Randomized, Controlled, Multicenter Trial of Percutaneous Peripheral Nerve Stimulation (PNS) for the Treatment of Back Pain

Sponsor: SPR™ Therapeutics, Inc.
22901 Millcreek Blvd
Suite 500
Cleveland, OH 44122

Study Device: SPRINT® PNS System

FDA Clearance for SPRINT® PNS System: K181422; K202660, K211801, K223306

Initial Date and Version: [redacted]

Amendments Dates/Versions: [redacted]
4 April 2024

Confidential Information:
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Protocol Synopsis

Title	A Randomized, Controlled, Multicenter Trial of Percutaneous Peripheral Nerve Stimulation (PNS) for the Treatment of Back Pain
Study Nickname	The RESET Clinical Trial
Device (510k Cleared)	The SPRINT® Peripheral Nerve Stimulation (PNS) System
Study Design	Prospective Randomized, Controlled, Multicenter Post Market Study
Primary Study Objective	The objective of the proposed study is to compare the effectiveness of percutaneous PNS to standard interventional management for the treatment of back pain. [redacted]
Study Plan	**Individuals must have an average pain intensity score of ≥ 4 out of 10 to qualify.** Individuals who report chronic low back pain confined to the lower back will be considered for enrollment into the study. After obtaining informed consent, potential subjects will be evaluated for general eligibility. To qualify for enrollment in the study, individuals must report average pain intensity in the previous week of ≥ 4 out of 10 (Brief Pain Inventory-Short Form, Question #5). Subjects must have failed at least 2 previous types of LBP therapies (*e.g.*, medications, physical therapy, injections) to participate. **Subjects will be randomized into one of two groups: Treatment with SPR's percutaneous PNS System (Group #1) or Control, treatment with conventional management (*e.g.*, using radiofrequency ablation (RFA) or other standard interventional management, Group #2).** The individuals who satisfy the preliminary criteria will be asked to complete a 7-day baseline diary to record their daily "average pain" intensity (Question #5 on the BPI-SF). Individuals must report an average pain intensity of ≥ 4 averaged across the 7-day diary to qualify to continue participation. Subjects randomized to Group 1 will undergo a diagnostic medial branch block (MBB) and regardless of the results, will then receive peripheral nerve stimulation (PNS) via two fine-wire leads placed percutaneously to activate nerves innervating muscles of the lower back and connected to an external pulse generator PNS parameters will be adjusted to produce comfortable sensations and subjects will be instructed to use stimulation daily for eight weeks. Subjects randomized to Group 2 will receive standard treatment of care (e.g., lumbar radiofrequency ablation, spinal cord stimulation, surgery, etc) following diagnostic testing or procedures, as appropriate (e.g., diagnostic MBB). After 8 weeks of PNS, subjects in Group 1 will return to the clinic to have their lead(s) removed. Subjects in Group 2 are eligible to crossover to receive SPRINT and continue study participation after 12 months. The

	primary endpoint will be assessed at 3 months after treatment with PNS or standard interventional management. **Average pain intensity will be measured for up to 24 months following treatment.** Subjects will use numerical rating scales to record average pain intensity (BPI-5) and worst pain intensity (BPI-3) over the past 24 hours, and record daily analgesic medication usage each week at baseline, 1-, 2-, 3-, 6-, 9-, 12-, 18- and 24-months after treatment. The study will compare the efficacy of percutaneous PNS for the treatment of chronic low back pain to standard interventional management for the treatment of chronic low back pain, by evaluating if the treatment effect is equivalent (*i.e.,* statistically non-inferior), and if so, if it is superior. [redacted]
Sites (N)	Up to 30 sites
Subjects (N)	Up to 230 individuals will be randomized
Inclusion Criteria	• Age ≥ 21 years and ≤ 75 years • Able to understand and comply with study requirements and provide written informed consent • Chronic low back pain (*i.e.,* pain lasting longer than 6 months, where the vast majority and center of pain is in the lumbar region, L1-L5 vertebral levels) • Reports an average low back pain score ≥ 4 on a scale of 0-10 (BPI-5) • Previous use of at least two types of LBP therapies (e.g., medications, physical therapy, injections, etc.) • At least 4 weeks of stable pain treatment or medication as indicated by subject reported medication history (*i.e.,* no new treatments or change in medication for pain in the last 4 weeks) • Reports active health insurance coverage (*e.g.,* through commercial insurance, Medicare, Medicaid, Tricare)
Exclusion Criteria	• Radicular leg pain (*e.g.,* pain that spreads to the lower extremities) or referred pain outside the lumbar region (*e.g.,* sacral pain, hip pain) that is ≥ 4 on a scale of 0-10, BPI-5 • Pain in the thoracic or cervical region that is ≥ 4 on a scale of 0-10, BPI-5 • Pain from the sacroiliac joint, as determined by the Investigator • Signs of infection on or around the low back, or other conditions that increase risk to the subject in the opinion of the Investigator

	(*e.g.,* valvular heart disease that creates an infection risk, compromised immune system, history of recurrent skin infections) • Signs of serious underlying cause of low back pain as determined by the Investigator, (*e.g.,* cancer, chronic infection, referred visceral pain, metabolic bone disorder) • Deep brain stimulation (DBS) system, an implanted active cardiac implant, or any other implantable neurostimulator whose stimulus current pathway may overlap the Sprint Stimulator's current pathway • Anesthetic or corticosteroid injections in the low back (including trigger point, epidural, intrathecal, facet, or sacroiliac joint injections) within the last 3 months (not including a diagnostic medial branch block), or botulinum toxin (Botox) injection in the low back within the last 6 months • Prior radiofrequency ablation of the lumbar medial branches (L1-L5) within the last 6 months • Prior lumbar surgery • Clinically relevant stenosis of the central canal or foramina as determined by the Investigator (*e.g.,* symptoms of neurogenic claudication) • Greater than mild lumbar scoliosis (*i.e.,* > 20 degrees) • Condition that could impact response to percutaneous PNS (*e.g.,* fibromyalgia confirmed by a specialist, multiple sclerosis, spinal cord injury, or other neurological disease or damage to central or peripheral nervous system) • History of significant trauma to the lumbar spine or paraspinal musculature (*e.g.,* burst fractures or fracture dislocations) • Score of > 20 on the Beck Depression Inventory (BDI-II) • Average Pain Interference score < 4 using BPI-9 • Obese with a body mass index (BMI) > 40 • Current illicit substance abuse or high-dose opioid dependence (*e.g.,* daily opioid usage ≥ 90 mg morphine equivalents) • Current participation, or less than 30 days from completing any drug or device trial, or previously received SPRINT for LBP • Pending litigation, workers compensation or other secondary gain issues • Tape or adhesive allergy • Allergy to all local anesthetic agents (*e.g.,* lidocaine) • Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator (*e.g.,* bipolar disorder) • Vulnerable populations (*e.g.,* prisoners, individuals that report to investigators) • Bleeding disorder (*e.g.,* hemophilia)

Additional Inclusion Criteria	• *Assessed before randomization:* Average pain intensity score of ≥ 4 (determined by calculating the mean "average pain" collected in a 7-day baseline diary, using Question #5 on the BPI-SF)
Additional Exclusion Criteria	• *Assessed before start of treatment:* Pregnancy (Group #1 only)
Primary Safety Endpoint	Occurrence and type of study-related adverse events.
Primary Clinical Endpoint	Clinically significant reduction in chronic low back pain as evidenced by ≥50% reduction in "average pain intensity" (BPI-5) 3 months after start of treatment (*i.e.,* average of weekly diary) compared to baseline (*i.e.,* average of baseline diary). • The primary endpoint compares the proportion of subjects in Group 1 (PNS) relative to that in Group 2 (Control) that achieve ≥ 50% reduction in average back pain intensity from baseline to 3-month follow up. This endpoint will examine the statistical non-inferiority of the proportion of clinical successes in Group 1 compared to Group 2, and if non-inferiority is achieved, examine the statistical superiority of the proportion of successes in Group 1 compared to Group 2.
Secondary Endpoints	Several secondary endpoints will be collected to evaluate what effect, if any, the interventions have on each measure. Unless specified, secondary efficacy endpoints for the following outcome measures will be assessed at 3 months after start of treatment. • Proportion success evidenced by 30% reduction in pain interference as measured using Question #9 of the BPI-SF (BPI-9) compared to baseline • Proportion with clinically significant change (≥ 10-point reduction) in disability as measured using the Oswestry Disability Index (ODI) compared to baseline • Durability of primary endpoint (proportion success with 50% reduction in average back pain intensity) at 6- to 24-months after treatment • Proportion success with 50% reduction in worst back pain intensity as measured using Question #3 of the BPI-SF (BPI-3) compared to baseline • Average Patient Global Impression of Change (PGIC) • Average change in health-related quality of life as measured using the EQ-5D compared to baseline • Average change in analgesic medication usage

Exploratory Measurements	[redacted]

Table of Contents

1.0 GENERAL INFORMATION

1.1. Title of the Investigation

A Randomized, Controlled, Multicenter Trial of Percutaneous Peripheral Nerve Stimulation (PNS) for the Treatment of Back Pain

1.2. Study Nickname

In addition to the formal study title above, this trial may also be referred to as The RESET Clinical Trial. Additional variations on this nickname may include The RESET RCT and The RESET Low Back Pain Study.

1.3. Sponsor Name and Address

SPR Therapeutics, Inc.
22901 Millcreek Boulevard, Suite 500
Cleveland, OH 44122
Phone: 216-378-9108
Fax: 216-378-9116

1.4. Name of the Device

The SPRINT® Peripheral Nerve Stimulation (PNS) System

1.5. Indication for Use

[redacted]

1.6. Study Objective

The objective of the proposed study is to compare the effectiveness of percutaneous PNS to standard interventional management for the treatment of back pain. [redacted]

2.0 BACKGROUND AND JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

Chronic LBP is a substantial medical problem

Chronic LBP is a substantial medical problem and a growing socioeconomic burden (1). Chronic LBP affects approximately 10% of the U.S. population and is the second leading cause of disability (2). Chronic LBP is associated with reduced activities of daily living, reduced quality of life, and a cost of $100-200 billion/year in the U.S. for treatment, missed workdays and reduced productivity (3-5). LBP has a global prevalence of approximately 12% and is likely to increase substantially in the future as the population ages (6). Further,

the direct medical costs associated with LBP represent only a small portion of the total costs of LBP, suggesting that therapies that reduce disability may also offer significant societal cost savings (1), in addition to improvements in quality of life for the individuals.

Acute LBP is characterized as pain lasting 3-6 weeks and usually resolves, although pain recurrences are common after the initial episode of acute LBP (7). Chronic LBP lasts > 12 weeks and is typically associated with greater pain intensity scores and bilateral pain (as opposed to unilateral or radiating pain) (8), and may be complicated by psychosocial dysfunction (9). Chronic low back pain is confined to pain in the low back area and usually caused by anatomical lesions (e.g., degenerated or herniated intervertebral discs) or damage to soft tissues (e.g., muscles, ligaments, or tendons).

Other treatments for chronic low back pain are ineffective, not well tolerated or associated with side effects and complications

Analgesics: Oral medications (e.g., acetaminophen, NSAIDs, muscle relaxants, tricyclic antidepressants, antiepileptics, corticosteroids) provide only limited and/or short-lived pain relief, and typically produce side effects (e.g., sedation, gastrointestinal problems) (10, 11). Although analgesics can provide substantial pain relief in some (52-55% of patients fail to experience sufficient pain relief (12, 13)), long-term use is not recommended (e.g., to prevent opioid dependence (11)).

Physical Therapy or Exercise: Physical therapy (PT), including strength training, may be capable of targeting both the physical dysfunction and pain. Exercise (including yoga, stretching, strength training) has a low level of risk and can relieve pain and improve function long-term, but patients often fail to comply with treatment regimens due to discomfort, lack of motivation, and inconvenience (14, 15). Studies have shown that when subjects are motivated and compliance is high with PT or exercise, chronic LBP and disability are significantly reduced, which is why PT is a common first-line therapy and currently the standard of care (16, 17). Unfortunately, many patients generally fail to comply with prescribed treatment regimens (14, 15) (≥50% have poor compliance attending PT sessions or completing home exercises (18)), resulting in a return of pain and dysfunction (19) and the need for an alternative first-line treatment for pain specialists to provide for chronic LBP.

Physical manipulation: Physical manipulation (e.g., massage, spinal manipulation) has a low level or risk and can provide short-term pain relief (20, 21). However, frequent treatment sessions are required to maintain pain relief, which is expensive and inconvenient for patients (22). Further, clinical studies on physical manipulation treatments have been poorly controlled.

Injections: Injections of steroids or anesthetic provide short-term pain relief but do not produce long-term benefit. As well, injections produce side effects and complications, including increased pain, lightheadedness, headache, infection, and nausea and vomiting (23-25).

Acupuncture: Acupuncture is minimally-invasive, and studies have suggested that acupuncture can provide pain relief and improvements in function (26). However, the adequacy of sham (placebo) controls in acupuncture studies has been questionable, and the effectiveness of acupuncture remains controversial (27).

Intrathecal Therapy: Intrathecal drug delivery is effective for reducing pain and improving function long-term (28) but requires an invasive procedure and is limited by a host of frequent side effects (e.g., nausea, infection, intrathecal granuloma) (29). Also, technical complications (i.e., problems with catheter or pump) are common and may require reoperation or removal of the device (30).

Surgery: Surgical procedures for back pain (spinal fusion, disc replacement) have become a common treatment of chronic LBP following failure of nonsurgical pain management (Munoz et al. 2016). Fusion is controversial, but has been found to be more efficacious than nonsurgical care in some cases of chronic intractable back pain (Hagg 2003, Fritzell 2005). However, alternative treatments are needed because surgery is highly invasive, irreversible, and carries risks of complications (31, 32) and frequently requires reoperation (31-33). Other types of back surgery (e.g., laminectomy, spinal decompression, discectomy) are typically indicated for radicular pain.

Transcutaneous electrical nerve stimulation (TENS): TENS has been investigated as a method of relieving chronic LBP (34). Although TENS is a widely accepted method of relieving some types of pain, there is limited evidence that it is effective at relieving chronic low back pain (35-37). In addition, stimulation intensity during TENS is often limited due to the activation of cutaneous nerve fibers, which can cause discomfort and irritation. Because stimulation intensity is limited during TENS, the therapy delivered may be suboptimal.

Radiofrequency Ablation (RFA): Lumbar RFA is a commonly used intervention for the treatment of chronic axial low back pain. RFA uses high frequency electrical current to ablate or lesion nerves to stop transmission of pain signals. In the low back, RFA is commonly performed on the medial branch of the dorsal ramus, which innervates the facet joints, paraspinal muscles, and skin of the low back. RFA can provide months of relief in properly selected patients (e.g., those receiving significant pain relief from diagnostic anesthetic injections or medial branch blocks), but results are highly dependent on physician expertise and approach, and are often followed by an eventual return of pain(38). Further, the destruction of nerves and recurrence of pain is a significant concern for younger populations suffering from chronic low back pain (*i.e.,* military service members, athletes).

Spinal cord stimulation (SCS): SCS has long been investigated for the treatment of low back pain (39), but successful pain relief varies greatly with back pain category and across different studies. SCS parameters can be difficult to program for sufficient pain relief (40) and SCS is historically less effective for predominant back pain than leg pain (41, 42). SCS is associated with complications following the invasive stimulation implant procedure, up to 43% of patients reported complications (43) and reoperation is often

required to reposition the lead, or for other technical complications, including damage to the lead or system failure (29, 44, 45). Because of the invasiveness, cost, and risk of device- and procedure-related complications, SCS is often reserved as a treatment of last resort.

Other Therapies: Other therapies (laser therapy, orthotics, thermal therapies, traction, ultrasound, lidocaine patch) are only useful for mild or non-chronic (<12 weeks) pain, controversial, and/or investigational.

Summary

Chronic low back pain is a significant problem and other current therapies for treatment are ineffective or associated with side effects and complications. Percutaneous peripheral nerve stimulation (PNS) has been shown to relieve LBP, while improving disability and quality of life. The proposed study will determine if the safety and effectiveness of percutaneous PNS is equivalent (and if so, if it is superior) to that of standard interventional management and determine if PNS produces clinically significant

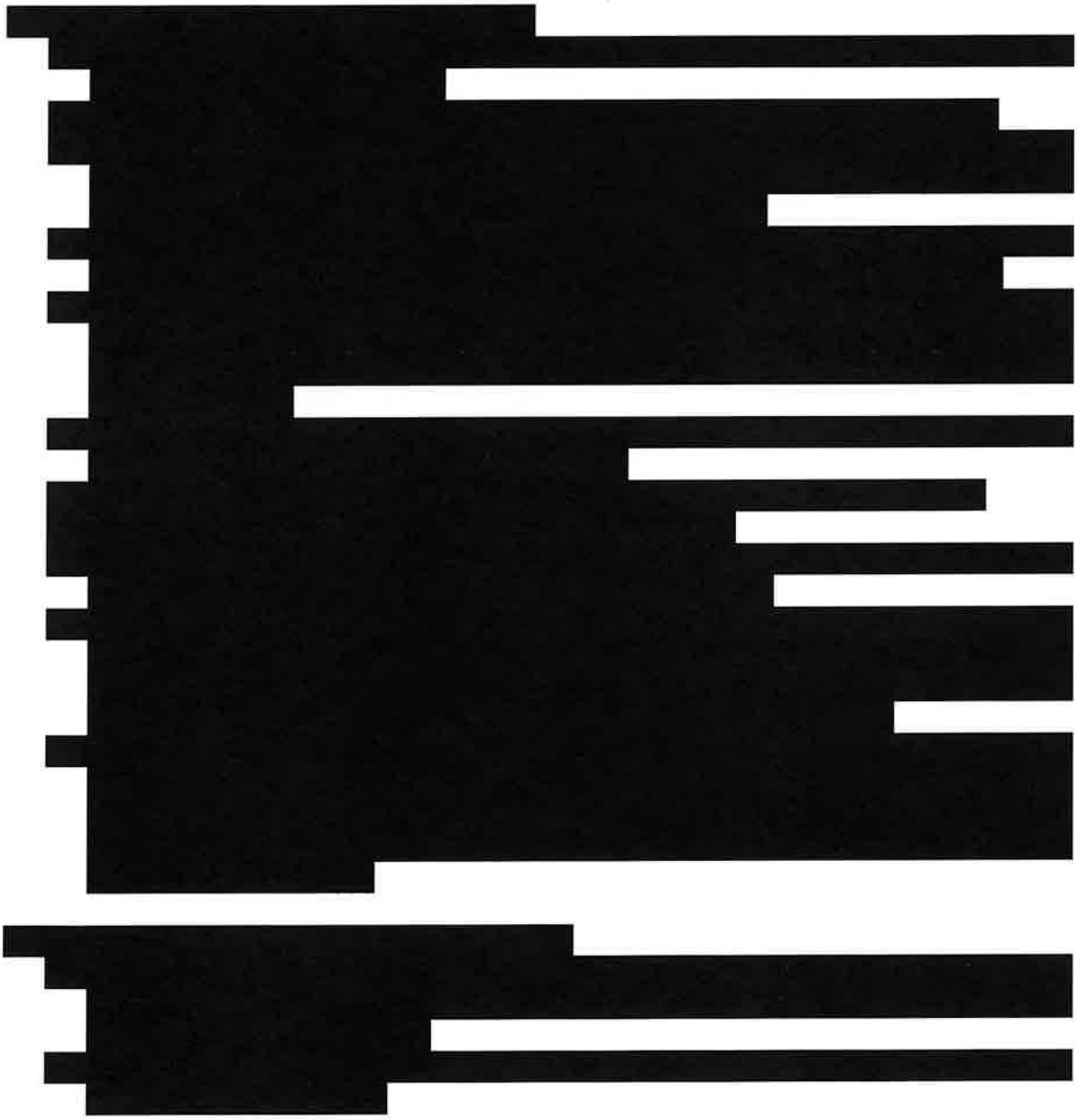
reductions in back pain, disability, and other key patient-centric outcomes.

3.0 DEVICE DESCRIPTION

This study utilizes the commercially available SPRINT® PNS System. [redacted]

3.1. System Component Overview

[redacted]



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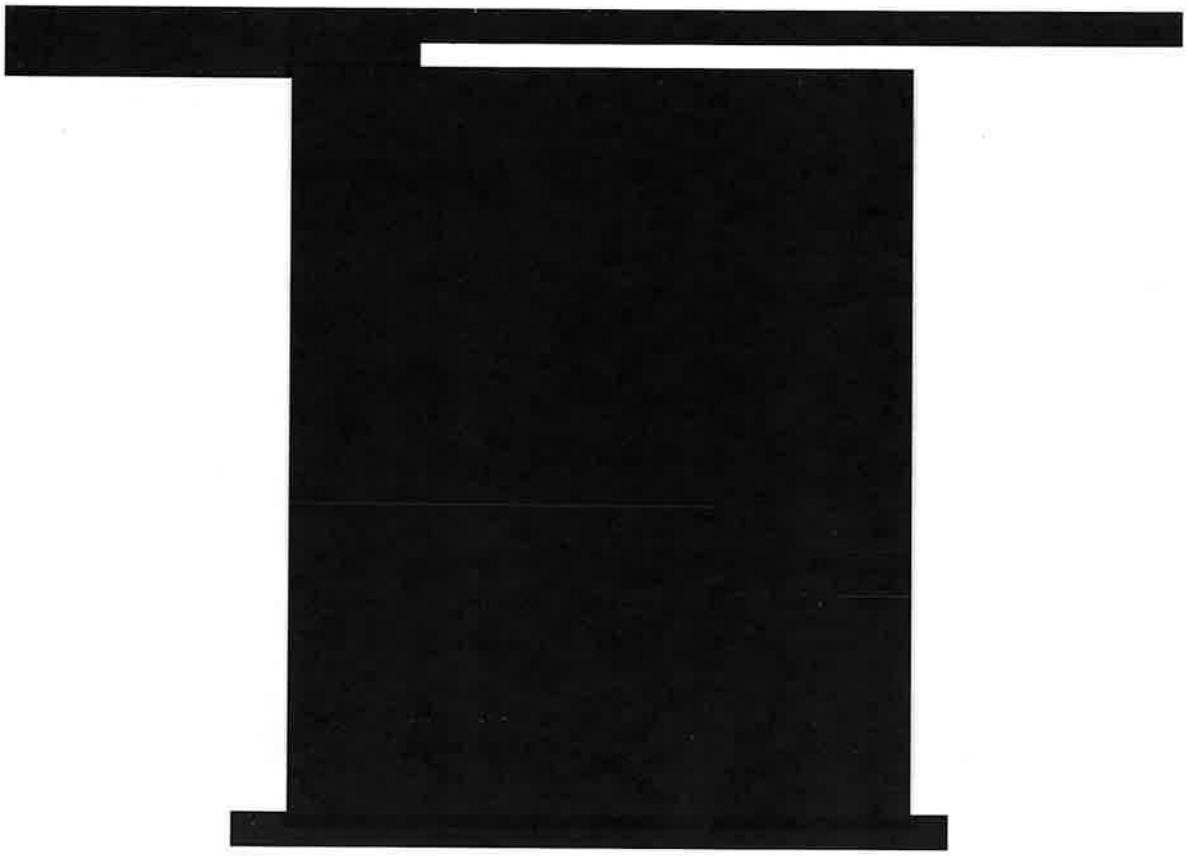


4.0 STUDY DESIGN

4.1. General Overview

This study is a post-market randomized controlled trial to compare the safety and effectiveness of percutaneous PNS for the treatment of low back pain to standard interventional management (e.g., radiofrequency ablation, RFA; spinal cord stimulation, SCS, surgery, etc). The treatment of chronic pain in the back is included in the indication statement for SPRINT PNS (K181422, K211801). This study will compare the efficacy of percutaneous PNS for the treatment of chronic low back pain to standard interventional management for the treatment of chronic low back pain, by evaluating if the treatment effect is equivalent (i.e., statistically non-inferior), and if so, if it is superior.

4.2. Subject Population

Prospective subjects will be screened for eligibility into the study using the Eligibility criteria listed in Section 4.2.1.

4.2.1. Selection Criteria

Inclusion Criteria

- Age ≥ 21 years and ≤ 75 years
- Able to understand and comply with study requirements and provide written informed consent
- Chronic low back pain (*i.e.,* pain lasting longer than 6 months, where the vast majority and center of pain is in the lumbar region, L1-L5 vertebral levels)
- Reports an average low back pain score ≥ 4 on a scale of 0-10 (BPI-5)
- Previous use of at least two types of LBP therapies (e.g., medications, physical therapy, injections, etc.)
- At least 4 weeks of stable pain treatment or medication as indicated by subject reported medication history (*i.e.,* no new treatments or change in medication for pain in the last 4 weeks)
- Reports active health insurance coverage (*e.g.,* through commercial insurance, Medicare, Medicaid, Tricare)

Exclusion Criteria

- Radicular leg pain (*e.g.,* pain that spreads to the lower extremities) or referred pain outside the lumbar region (*e.g.,* sacral pain, hip pain) that is ≥ 4 on a scale of 0-10, BPI-5
- Pain in the thoracic or cervical region that is ≥ 4 on a scale of 0-10, BPI-5
- Pain from the sacroiliac joint, as determined by the Investigator
- Signs of infection on or around the low back, or other conditions that increase risk to the subject in the opinion of the Investigator (*e.g.,* valvular heart disease that creates an infection risk, compromised immune system, history of recurrent skin infections)
- Signs of serious underlying cause of low back pain as determined by the Investigator, (*e.g.,* cancer, chronic infection, referred visceral pain, metabolic bone disorder)
- Deep brain stimulation (DBS) system, an implanted active cardiac implant, or any other implantable neurostimulator whose stimulus current pathway may overlap the Sprint Stimulator's current pathway
- Anesthetic or corticosteroid injections in the low back (including trigger point, epidural, intrathecal, facet, or sacroiliac joint injections) within the last 3 months (not including a diagnostic medial branch block), or botulinum toxin (Botox) injection in the low back within the last 6 months
- Prior radiofrequency ablation of the lumbar medial branches (L1-L5) within the last 6 months
- Prior lumbar surgery
- Clinically relevant stenosis of the central canal or foramina as determined by the Investigator (*e.g.,* symptoms of neurogenic claudication)
- Greater than mild lumbar scoliosis (*i.e.,* > 20 degrees)
- Condition that could impact response to percutaneous PNS (*e.g.,* fibromyalgia confirmed by a specialist, multiple sclerosis, spinal cord injury)
- History of significant trauma to the lumbar spine or paraspinal musculature (*e.g.,* burst fractures or fracture dislocations)
- Score of > 20 on the Beck Depression Inventory (BDI-II)

- Average Pain Interference score < 4 using BPI-9
- Obese with a body mass index (BMI) > 40
- Current illicit substance abuse or high-dose opioid dependence (e.g., daily opioid usage ≥ 90 mg morphine equivalents)
- Current participation, or less than 30 days from completing any drug or device trial, or previously received SPRINT for LBP [redacted]
    - Note: subjects in the follow-up phase of a COVID-19 vaccine study will be allowed to participate in this study, provided the vaccine is cleared under a FDA Emergency Use Authorization or full FDA approval.]
- Pending litigation, workers compensation or other secondary gain issues
- Tape or adhesive allergy
- Allergy to all local anesthetic agents (*e.g.,* lidocaine)
- Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator (*e.g.,* bipolar disorder)
- Vulnerable populations (*e.g.,* prisoners, individuals that report to investigators)
- Bleeding disorder (e.g., hemophilia)
    - Note: anticoagulant use is not considered a bleeding disorder.

Additional Inclusion Criteria *(assessed before randomization)*
- Average pain intensity score of ≥ 4 (determined by calculating the mean "average pain" collected in a 7-day baseline diary, using Question #5 on the BPI-SF)

Additional Exclusion Criteria *(assessed before start of treatment)*
- Pregnancy (Group #1 only)

4.2.2. Recruitment of Target Population

Subjects with chronic low back pain will be recruited by the investigators, following all HIPAA guidelines, to ascertain their level of interest and willingness to take part in this study. Recruitment materials will be provided to aid in subject enrollment. All recruitment materials will be IRB approved prior to their use. A third-party clinical trial recruitment firm may also be used to support recruitment efforts, such as a toll-free patient information center.

4.2.3. [redacted]

4.2.4. [redacted]

4.2.5. Vulnerable Population

Vulnerable populations, such as prisoners, individuals that report to investigators, or children, are excluded from participation in this study (Section 4.2.1) and will not be enrolled.

4.2.6. Sample Size & Justification

Up to 30 sites will participate in the study. The study will be planned with a maximum sample size of 230 enrolled subjects [redacted] Subjects will be randomized to either Group #1 or Group #2 using a 1:1 randomization scheme.

All subjects who sign a consent will receive a subject ID number. Subjects who sign a consent and do not meet all study eligibility criteria will be considered screen failures and not count against the number of enrolled subjects. Subjects who are randomized at Visit 2 will be counted as enrolled. If a subject does not receive the randomized intervention (e.g., complete PNS or receive a standard interventional procedure), their results may be excluded and/or analyzed separately from the rest of the population.

4.2.7. Concurrent Medications and Non-Drug Therapies

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

Subjects will be permitted to use analgesic medications (opioid or non-opioid) as prescribed/recommended by their physician and analgesic usage will be recorded. However, to qualify for enrollment, their current medication or therapy history must have been stable for at least 4 weeks. Subjects will be asked to indicate the reason for use (e.g., back pain, or other pain such as headache, leg pain, toothache, etc.). Subjects using other therapies will continue to participate in the study visits, but will be asked to report the use of other therapies or changes in medications at study visits.

[redacted]

4.3. Study Endpoints

Outcomes and exploratory measures will be collected per Appendix B.

4.3.1. Primary Endpoints

4.3.1.1. Primary Efficacy Endpoint

The primary outcome of this study will be calculated as the mean score of average daily back pain intensity 3 months after start of treatment to baseline. This will be recorded using Question 5 of the Brief Pain Inventory Short Form (BPI-5; details of BPI below), which assesses "average pain" on an 11-point numerical rating scale, with one end

representing "no pain" (0) and the other end representing "pain as bad as you can imagine" (10). Subjects will record BPI-5 scores daily in a diary, and the mean score for each week will be calculated for each subject. The primary endpoint will be a highly clinically significant reduction in back pain evidenced by ≥ 50% reduction in mean "average pain" (BPI-5) over the week prior to the 3-month follow-up visit (Visit 13) compared to baseline.

The primary endpoint compares the proportion of subjects in Group 1 (PNS) relative to that in Group 2 (standard interventional management) that achieve ≥ 50% reduction in average back pain intensity from baseline to 3-months after start of treatment. This endpoint will examine the statistical non-inferiority of the proportion of clinical successes in Group 1 compared to Group 2, and if non-inferiority is achieved, examine the statistical superiority of the proportion of successes in Group 1 compared to Group 2. [redacted]

4.3.1.2. Primary Safety Endpoint

The primary safety endpoint is the occurrence and type of study-related adverse events. For Group 1 (PNS), all adverse device effects (ADEs) that occur during the study will be documented. For group 2 (standard interventional management), all study-related adverse events will be documented. For both groups, AEs related to standard of care (SOC) will be collected. Specific details regarding any study-related AE will be collected on an Adverse Event Form and will be followed to resolution. The investigator will determine the severity of each event as well as its relationship to the study (i.e., device and procedure). In addition, each event will be categorized as either serious or non-serious. Any necessary treatment or intervention required and the resolution status of the event will also be documented. Study-related AEs will be tabulated and summarized at the conclusion of study. Additional details on the monitoring and adjudication of study-related AEs is described in the section regarding monitoring.

4.3.2. Secondary Endpoints

Several secondary endpoints will be collected to evaluate what effect, if any, the interventions have on each measure. [redacted] Analyses may also explore the effect of the actual intervention(s) received on these secondary endpoints. Secondary efficacy endpoints for the following outcome measures will be assessed at 3 months after start of treatment, unless otherwise stated:

- Proportion success evidenced by ≥30% reduction in pain interference as measured using Question #9 of the BPI-SF (BPI-9) compared to baseline
- Proportion with clinically significant change (≥ 10-point reduction) in disability as measured using the Oswestry Disability Index (ODI) compared to baseline
- Durability of primary endpoint, proportion success with ≥50% reduction in average back pain intensity, at 6- to 24-months after start of treatment
- Proportion success with ≥50% reduction in worst back pain intensity as measured using Question #3 of the BPI-SF (BPI-3) compared to baseline
- Average Patient Global Impression of Change (PGIC)

- Average change in health-related quality of life as measured using the EQ-5D compared to baseline
- Average change in analgesic medication usage (e.g., opioids, non-opioids, and total analgesic medication usage)

Brief Pain Inventory-Short Form (BPI)

The BPI is a widely used assessment designed to measure pain intensity and the interference of pain on daily activities and moods (Cleeland and Ryan 1994). The BPI is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) panel and has demonstrated validity and reliability across many cultures and languages (51, 52). 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. Individual questions of the BPI (e.g., "average pain" (BPI-5), "worst pain" (BPI-3), and "pain interference" (BPI-9)) may be assessed during visits at various time points, including: baseline, follow-up visits, and take-home diaries. When answering BPI questions, subjects will be asked in the question to focus on their back pain or other pain (e.g., leg pain). The site may make arrangements as needed to collect BPI scores if subjects fail to submit their responses (e.g., call to remind the subjects to complete or turn in their diary, mail paper or electronic diaries for BPI question completion, or call and ask questions from the BPI verbally).

Oswestry Disability Index (ODI)

The ODI is a short, widely used assessment designed to measure the degree of disability in patients with low back pain. This validated questionnaire includes topics concerning the intensity of pain, the subject's ability to perform normal daily activities such as personal care, walking, sitting, or standing, and how pain affects the subject's sex life, social life, and travel (53). The ODI will be administered at baseline and follow-up visits. This assessment will provide important information on how disability caused by pain changes during and after treatment with stimulation or standard treatment with RFA.

Health-related quality of life (EQ-5D)

The EQ-5D survey is a standardized instrument measuring health-related quality of life and generic health status. The health status description is measured in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and the evaluation asks responders to report their overall health status on a visual analog scale (VAS). The EQ-5D is one of the most commonly cited preference based measures and becoming the gold standard for cost-effectiveness and value assessment (Chapman et al. 2011). The EQ-5D will be assessed at baseline and follow-up visits.

Patient Global Impression of Change (PGIC)

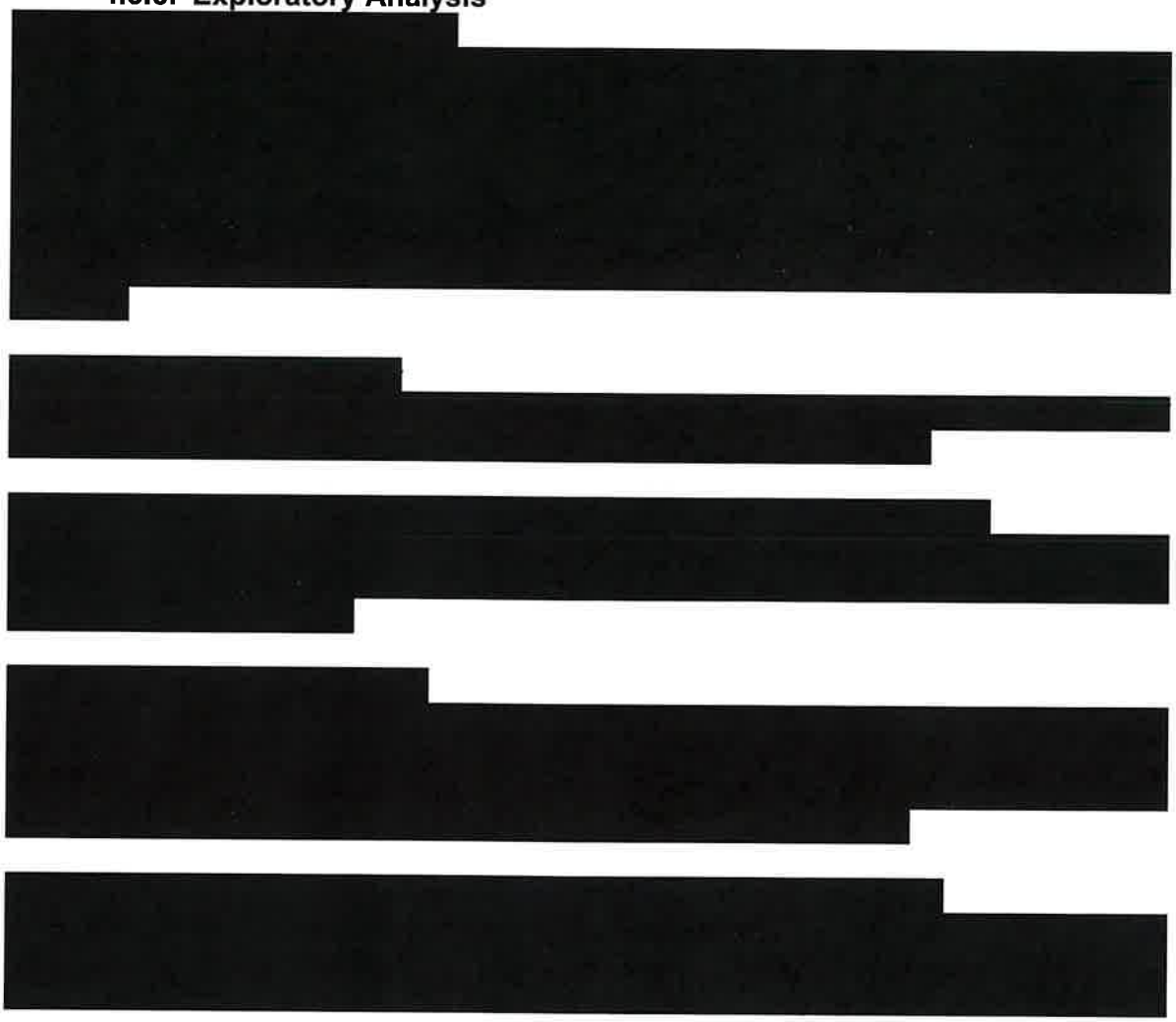
Participant ratings of global improvement are one of the core outcome domains in chronic pain studies (52). The Patient Global Impression of Change (PGIC) Scale will be administered at monthly follow-up visits to assess subject perception of overall improvement. The PGIC Scale asks subjects to rate their 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.

Analgesic medication usage

The amount and type of analgesic used by the subject will be recorded daily in diaries at baseline and during the week of each follow up visit. Specific analgesic information that will be collected may include dosages of all narcotic or non-narcotic analgesic pain medications. Narcotic usage may be converted into a morphine equivalent dosage (MED). The use of any other methods of pain relief will also be recorded. This information will be used to assess any changes in medication usage required by the subject and average changes in medication between groups. Opioid, non-opioid and total analgesic medication usage will be analyzed separately.

4.3.3. Exploratory Analysis



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[redacted]

[redacted]

4.4. 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.

[redacted]

5.0 STUDY PROCEDURES

The study procedures for this protocol are classified according to the following time periods: Consent/Baseline; Diagnostic Procedures and Treatment; and Follow up. Appendix A provides a summary of the study design and overview of subject participation flow. Appendices B.1-B.3 provide a schedule of the study procedures. Appendix C includes the subject participation flow chart

[redacted]

5.1. Visit 1 – Consent

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

The consent form will be kept with the study records, and a copy of the consent will be given to the subject. A notation should be made in the subject's medical record of participation in the study, and a copy of the consent may be placed in the hospital record.

The following measures will be assessed:

- Selected questions from Brief Pain Inventory (BPI) (e.g., BPI-3, BPI-5, BPI-9)
- Oswestry Disability Index (ODI)
- Health-related quality of life (EQ-5D)
- Low back pain treatment and diagnostic testing history [redacted]
- [redacted]
- Beck Depression Inventory (BDI-II)
- [redacted]
- [redacted]
- Key demographic information

A weekly diary will be distributed at this visit for daily recording of baseline back pain via "average pain" (BPI-5), "worst pain" (BPI-3), and analgesic usage prior to randomization. Subjects may be contacted to be reminded of the upcoming Visit 2 date and to review the baseline diary for contents and completion.

5.2. Visit 2 – Randomization

Visit 2 will be conducted upon completion of the baseline diary. The following measure will be assessed:

- Selected questions from Brief Pain Inventory (BPI) (e.g., BPI-3, BPI-5)

Randomization will occur after the following criterion has been met:

- All subjects must have completed all 7 days of the 7-day baseline diary to be eligible to continue participation in the study. The mean "average pain" (BPI-5) score from this diary will be calculated to confirm eligibility (i.e. "average pain" ≥ 4) prior to randomization. If the calculated mean "average pain" from the first week diary is < 4, the subject will be considered a screen failure, excluded from the study, and will not proceed with the remainder of the visit or study. The diary may be collected either in-person, by mail/email, or completed electronically. If the diary

is collected electronically or by mail/email, Visit 2 may be completed over the phone.

Subjects who meet this additional inclusion criterion will be considered eligible for the study. Qualifying individuals will be randomized in a 1:1 scheme using block randomization to Group 1 (8 weeks of percutaneous PNS therapy following MBB) or Group 2 (standard interventional management). [redacted]

Following randomization and completion of Visit 2, all subjects will return to receive a medial branch block or other diagnostic procedure, as appropriate (named Visit 3), before progressing to receive their randomized treatment at Visit 4 (*i.e.,* either SPRINT PNS lead placement for Group 1 or standard interventional management (e.g., RFA, SCS, surgery, etc.) for Group 2.

5.3. Visit 3 – Medial Branch Block or Diagnostic Procedures

A diagnostic medial branch block (MBB) or other diagnostic procedure (e.g., SCS trial, imaging, etc.), as deemed appropriate by the physician for subjects in Group 2, will be completed at or following Visit 3. Visits 2 and 3 may occur on the same day.

The following measures will be assessed at this visit for both groups:

- Selected questions from Brief Pain Inventory (BPI) (e.g., BPI-3, BPI-5)
- Current pain treatments/analgesic usage

GROUP 1 – Medial Branch Block

Subjects will undergo a standard diagnostic medial branch block (MBB) targeting the area where they have chronic low back pain. Provocative maneuvers or positions which normally exacerbate their typical pain may also be assessed and documented before and after the procedure to help determine effect of MBB.

The diagnostic medial branch block (MBB) will be performed according to standard practice using aseptic technique. [redacted]

Pain scores will be collected post-procedure to evaluate the impact of the MBB. Subjects in Group 1 (PNS) will proceed to Visit 4 (PNS Lead Placement) after a single MBB (Visit 3), regardless of the outcome.

If a subject has previously undergone a diagnostic lumbar medial branch block (MBB) within 3 months of the baseline visit, and results and medical records are available from that block, a subject is not required to complete an additional block at this visit. However, procedure details and results from the procedure should be documented in the CRFs. If a subject previously underwent the MBB and results are not available, the subject should complete the visit, repeating the MBB as part of the study.

GROUP 2 - Diagnostic Procedures
Subjects in Group 2 will receive standard of care diagnostic testing and/or interventions (e.g., Medial Branch Block, SCS trial, MRI, etc.) for their low back pain as they usually would if not participating in the study. All diagnostic tests or interventions received by Group 2 subjects will not be paid for through the study. Subjects should follow their insurance requirements (e.g., prior authorization) for these procedures. [redacted] Additionally, for subjects in Group 2, another MBB or other diagnostic procedure may be repeated at a repeat Visit 3, if necessary. The necessity of a second Visit 3 will be determined by the Investigator and/or subject's Insurance, as is required for them to receive the randomized therapy (standard interventional management deemed appropriate by the investigator).

If a subject has previously undergone a diagnostic procedure (e.g., MBB, MRI, SCS trial, etc. within 3 months of the baseline visit, results and information may be collected to serve as diagnostic procedures completed for Visit 3.

Details will be collected regarding the approaches used for the diagnostic procedure(s), as well as outcomes following the procedure(s), including adverse events.

Subjects in Group 2 will continue to participate in the study visits independent of their successful completion of diagnostic procedures and/or standard interventional management. For example, if a subject does not proceed to receive lumbar RFA because they failed their MBB (e.g., had less than 50% response), they may receive other treatments for their low back pain recommended by their physician and continue to participate in study visits. In this case, the subject will still return to the clinic at Visit 4 to discuss alternative standard interventional management approaches, which will be regarded as the start of Treatment.

5.4. Visit 4 – Treatment (PNS Lead Placement or start of treatment with Standard Interventional Management)

GROUP 1 - PNS Lead Placement
Subjects randomized to Group 1 will undergo the following prior to lead placement:

- Women of childbearing age and reproductive potential will have a pregnancy test completed as part of eligibility confirmation before or at Visit 4.

- Subjects taking anticoagulants may have their medication adjusted as determined by the Investigator to prevent potential excessive bleeding.

Participants who are randomized to Group 1 and meet all Eligibility criteria will undergo placement of the percutaneous leads. The following measures may be assessed prior to lead placement:

- Selected questions from Brief Pain Inventory (BPI) (e.g., BPI-3, BPI-5)
- [redacted]
- Current pain treatments/analgesic usage

[redacted]

Figure 2 shows a magnetic resonance image (MRI) of the spine and paraspinal musculature.

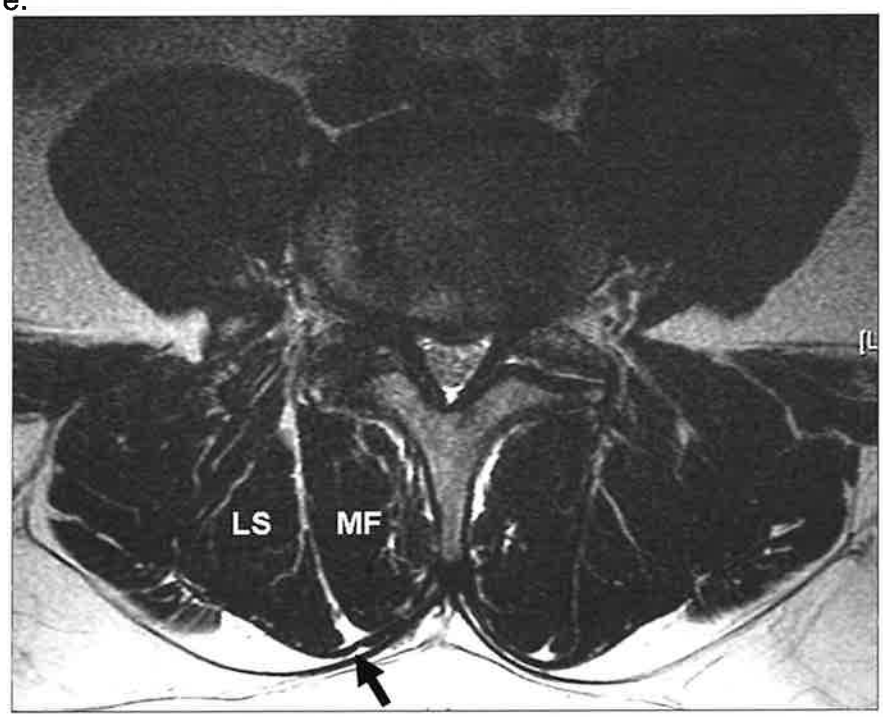


Figure 2: Magnetic resonance image (MRI) of lumbar paraspinal musculature, multifidus (MF) and longissimus (LS) (54).

The most painful regions on each side of the subject's back may be determined [redacted] The relevant section of the back will be cleansed and draped using aseptic technique and will not be shaved (cutting hair with scissors or clippers will be

allowed). Local anesthesia may be administered at the insertion site prior to lead placement.

[redacted]

Placement of the leads will be guided by use of ultrasound or fluoroscopy.

[redacted]

[redacted]

Leads will be placed in the lumbar region

to target the medial branch of the dorsal ramus

[redacted]

[redacted]

Determination of stimulation parameters:
Stimulus parameters will be varied over a range of parameters [redacted] Stimulation intensities will be delivered within ranges that have been demonstrated not to cause tissue damage [redacted]. Optimal stimulus settings will be set by the site staff prior to the end of the visit (Visit 4) and may be adjusted as needed throughout the study.

[redacted]

[redacted]

Stimulation parameters may be varied. [redacted] Safeguards on the device ensure the subject cannot exceed the acceptable safety ranges for stimulation. The care and

maintenance of the stimulation system, leads, and lead exit sites will be performed by members of the clinical or study staff. Subjects will also be provided with a manual and instructed on the use and care of the device in case changes are required when clinical/study staff is not present. Subjects will be encouraged to enlist assistance from a caregiver for monitoring skin and changing bandages. However, subjects may also request visits to the clinical site for monitoring of skin and/or bandage changes by study staff.

Sterile, waterproof covering bandages [redacted] will be placed over the exit sites of the leads. [redacted] The clinical/study staff and subject will be instructed to inspect the electrode exit site for signs of irritation and report them to the clinician. [redacted]

The area around the leads and surface electrodes will be kept clean and dry. If bandages become wet or loose, the bandages will be changed. [redacted]

[redacted]

[redacted]

[redacted]

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

GROUP 2 - Standard Interventional Management
Subjects in Group 2 will receive standard interventional management for the treatment of their low back pain, as usual, at the discretion of the site investigator. Visit 4 is not required to be completed on the exact day of the intervention; subjects may return for the visit on a separate day.

The following measures will be assessed:

- Selected questions from Brief Pain Inventory (BPI) (e.g., BPI-3, BPI-5)
- [redacted]
- Current pain treatments/analgesic usage

Details will be collected regarding the approaches used for intervention (e.g., system manufacturer, parameters, location, etc), as well as outcomes following the procedure. Subjects in Group 2 will continue to participate in the study visits independent of their successful completion of diagnostic testing and/or standard interventional management procedure(s) (i.e., even if a subject does not proceed to receive RFA, SCS, or surgery, they may continue to participate in study visits).

It is possible that treatment with standard interventional management may not be completed at this visit (e.g., if multiple nerves and/or levels are to be ablated with RFA during the procedure, or additional treatments or procedures are required). Thus, at the conclusion of this Visit, a subject will proceed to treatment phase. The subject will receive care as usual following the procedure and return for study visits according to the visit schedule. The subject may return as needed to complete additional diagnostic or interventional procedures throughout the study. In this scenario, the subject will still maintain the schedule of visits starting from the first Visit 4.

Subjects may elect not to undergo a diagnostic procedure and/or treatment (*e.g.,* subject elects to continue their usual care for back pain) but are still willing to remain in the study. In this event, if the subject has not undergone a diagnostic procedure by the end of the Visit 3 window, they will progress directly to Visit 4 (i.e., Visit 3 will be marked as "missed" and Visit 4 will be completed via phone). Regardless of the mode of participation, subjects who continue participation through 12 months after "Start of Treatment" (completion of Visit 16) will be eligible for crossover.

Subjects in Group 2 who receive standard interventional management may be eligible to receive treatment with PNS as part of the study via crossover after 12 months (Visit 16).

5.5. Visits 5-11: Weeks 1 through 7 after Treatment

During the early phase of visits after Visit 4 (PNS lead placement or standard intervention), follow-up visits will take place weekly, either in person or over the phone, and will occur as follows:

	GROUP 1		GROUP 2	
Visit	**In Clinic**	**Telephone**	**In Clinic**	**Telephone**
Visit 5 (1 week)	X			X
Visit 6 (2 weeks)	X			X
Visit 7 (3 weeks)		X		X
Visit 8 (4 weeks /1 month)	X		X	
Visit 9 (5 weeks)		X		X
Visit 10 (6 weeks)	X			X
Visit 11 (7 weeks)		X		X

During these visits, all subjects will be queried for study-related adverse events and lead exit sites will be inspected in Group 1. Outcome measures will be administered according to the schedule of procedures (Appendix B).

At Visit 4 and Visit 8 weekly diaries will be distributed for daily recording of "average pain" (BPI-5), "worst pain" (BPI-3), and analgesic usage prior to the next in clinic visit and to be turned in at that time (*e.g.,* Visit 8 or Visit 12). If a diary is lost or not returned at the visit, a diary for that visit may be completed by the patient after the visit and returned (e.g., via mail/email). Adjustment of stimulation parameters may be performed for Group 1, as determined by the site staff.

If necessary (e.g., to minimize missing data or encourage subject compliance), study staff may make arrangements to reduce burden of study participation on a subject. If a subject is unable to return to the clinic for a visit, options to collect the most important assessments (e.g., pain intensity, ODI) and data (e.g., LBP treatment use, adverse events, etc.) will be made available to the subject (e.g., assessment of surveys and visit questions via phone or video call, remote completion of surveys via mail, email, ePro, etc.). [redacted]

5.6. Visit 12: 8 weeks after Treatment

Visit 12 will occur 8 weeks (2 months) after Visit 4 (Treatment). At this visit, subjects in Group 1 will discontinue use of the stimulation therapy and have leads removed. Percutaneous leads must be removed within 60 days of lead placement for Group 1 subjects. All subjects will be queried for adverse events and lead exit sites will be inspected in Group 1. Additional outcome measures will be administered according to the schedule of procedures (Appendix B).

At this visit, the previous weekly diary will be collected and a new weekly diary will be distributed for daily recording of "average pain" (BPI-5), "worst pain" (BPI-3), and analgesic usage prior to the next visit (Visit 13). If a diary is lost or not returned at the

visit, a diary for that visit may be completed by the patient after the visit and returned (e.g., via mail/email). If a subject is unable to return to the clinic for a visit, options to collect the most important assessments (e.g., pain intensity, ODI) and data (e.g., LBP treatment use, adverse events, etc.) will be made available to the subject (e.g., assessment of surveys and visit questions via phone or video call, remote completion of surveys via mail, email, ePro, etc.).

At the conclusion of this visit, Group 1 subjects' leads will be removed by gentle traction

[redacted]

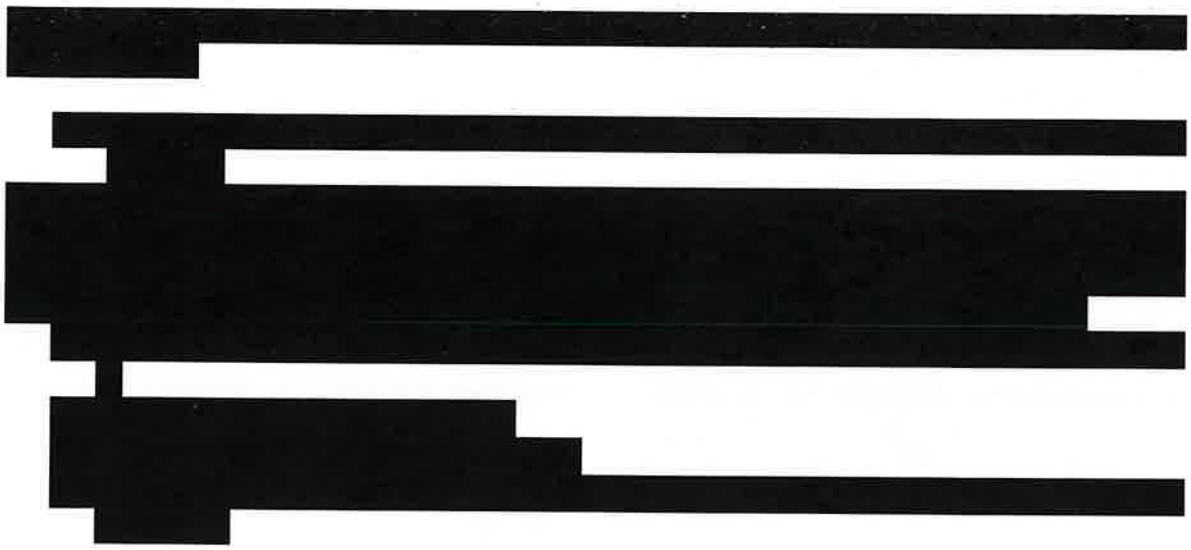
5.7. Follow up Visits: Visits 13 (3 month), Visit 14 (6 months), Visit 15 (9 months), Visit 16 (12 months), Visit 17 (18 months), and Visit 18 (24 months)

Follow up visits will occur at 3, 6, 9, 12, 18, and 24 months (Visits 13-18) after Treatment (Visit 4; See Schedule of Visits in Appendix B). Outcome measures will be administered according to the schedule of procedures (Appendix B).

In accordance with the Schedule of Visits (Appendix B), diaries will be collected at each follow up visit. If a diary is lost or not returned at the visit, a diary for that visit may be completed by the patient after the visit and returned (e.g., via mail/email). Diaries for the next visit will be distributed, for daily recording of baseline "average pain" (BPI-5), "worst pain" (BPI-3), and analgesic usage for the week prior to the next visit. Alternatively, the diary may be mailed/emailed to the subject for completion prior to the next visit. To mitigate missing data, an unreturned diary may be replaced with weekly recall "average pain" (BPI-5), "worst pain" (BPI-3) from that visit. If the subject is unable to return to the clinic, the diary and questionnaires may be completed and returned via mail, or the information can be collected by the research staff in a telephone call. Further, if a subject is unable to return to the clinic for a visit, options to collect the most important assessments (e.g., pain intensity, ODI) and data (e.g., LBP treatment use, adverse events, etc.) will be made available to the subject (e.g., assessment of surveys and visit questions via phone or video call, remote completion of surveys via mail, email, ePro, etc.).

In addition, subjects will be queried for adverse events. If no ADEs are noted, the subject will be discharged from the study at the site following the 24-month visit. Any ADE will be documented, addressed, and followed to resolution.

[redacted]



5.9. Unscheduled Visits/Lead Replacements

Subjects in Group 1 may require an unscheduled visit if they experience a technical issue with the stimulation system that the clinical staff has difficulty resolving over the phone, desire adjustments to stimulation parameters, require a bandage change or lead replacement, or experience an ADE which requires further evaluation by the clinical study staff. In the event of a device deficiency [redacted], site staff should contact SPR personnel to report the event.

It is possible that the leads may migrate from the intended target location or may become fully dislodged. In the event that a lead migrates or become dislodged, the Investigator may elect to place another lead. Throughout the 8-week PNS therapy for Group 1, the protocol allows for additional lead placements as necessary. This decision will be at the discretion of the Subject, Investigator and the Sponsor and should take into account the following considerations:

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

If the subject does not desire to continue with additional lead placements, they may continue with the schedule of follow-up visits per protocol (based on the date of Visit 4). Any additional lead placements in Group 1 will involve additional instances of Visit 4 (described above) and the associated requirements (e.g., subjects who initially required a pregnancy test prior to the first lead placement will have the test repeated as necessary). Subjects will then receive the remaining balance of the stimulation therapy. Subjects will have an additional exposure to the risks of lead placement, but the risks are the same as the risks detailed for the initial procedure.

[redacted]

Subjects in Group 2 may return to the clinic for an unscheduled visit, as needed. Unscheduled visits do not need to be completed for each treatment/procedure; rather the information will be collected at the subject's next study visit. Subjects in Group 2 may also require an unscheduled visit if they experience a study related adverse event which requires further evaluation by the clinical study staff.

5.10. Study Visit Windows

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

Table 1 Study Visit Windows

Visit Number	Visit Name	[redacted]
1	Baseline	
2	Randomization	
3	Group 1: MBB Group 2: Diagnostic Procedure	
4	Lead Placement and Stimulation Programming (Group 1) / Standard Intervention (Group 2)	
5	1 week visit (Phone call for Group 2)	
6	2 week visit (Phone call for Group 2)	
7	3 week phone call	
8	4 week (1 month) visit	
9	5 week phone call	
10	6 week visit (Phone call for Group 2)	
11	7 week phone call	
12	8 week (2 month) visit (Lead Removal for Group 1)	
13	3 month follow up	
14	6 month follow up	
15	9 month follow up	
16	12 month follow up	
17	18 month follow up	
18	24 month follow up	
C1	Group 2: Crossover lead placement	
C2	Group 2: 4 week (1 month visit)	
C3	Group 2: 8 week (2 month visit) Lead Removal	
C4	Group 2: 3 month visit	
C5	Group 2: 6 month phone call	
C6	Group 2: 9 month phone call	
C7	Group 2: 12 month phone call	

5.11. Early Study Termination

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

5.12. Subject Crossover

Subjects randomized to the control group (Group 2) may crossover to receive PNS after 12 months (Visit 16). The ability to crossover may depend on Investigator judgement related to the interventional procedure the subject received (e.g., if it conflicts with the SPRINT Instructions for Use).

Group 2 subjects who crossover to receive PNS and complete Visit C1 (lead placement) will then complete study visits to collect outcomes at 1-mo (Visit C2), 2-mo (C3), 3-mo (C4), 6-mo (C5), 9-mo (C6), and 12-mo (C7) after PNS lead placement. Visits C5 through C7 will be completed as phone calls. Outcomes at all crossover visits will be assessed in accordance with Appendix B. Women of childbearing age and reproductive potential will have a pregnancy test completed before or at Visit C1.

[redacted]

Subjects who are randomized to Group 1 (PNS), but wish to also receive RFA or another standard interventional management may elect to undergo any other treatments for low back pain at any point, however, the use of other therapies or interventions will be collected at study visits. Subjects electing to receive other treatments will still continue participation as Group 1 subjects (i.e., are not discharged from study, continue participation in study visit schedule as normal, and are not crossed over to Group 2 for the purposes of the study).

5.13. Subject Compensation

Individuals who are not 1) federal employees [civil servants] or 2) active military duty personnel will receive [redacted] compensation for taking part in all study visits. Compensation will be based on the subject completing milestones within the study. Federal Employees (civil servants) or active military duty

personnel who are not off duty or on leave during study visits would not be eligible for compensation. The disbursement schedule will be as follows:

- [redacted] after the completion of Visit 1 – Consent
- after the completion of Visit 2 – Randomization
- after the completion of each Visit 3 – MBBs or Diagnostic Procedures
- [redacted] after the completion of Visit 4 – Lead placement and stimulation programming (Group 1) or standard interventional management (Group 2)
- [redacted] after the completion of each in-person early follow-up visit
- after the completion of each telephone call
- after the completion of each long-term follow-up visit

[redacted]

If a subject volunteers to participate in an additional Visit 4 (returns for another session of stimulation testing, lead replacement, or intervention), the subject will receive an additional [redacted] compensation at the completion of that visit. All requirements for Visit 4 will be repeated. If a Group 2 subject crosses over to receive the PNS system, they will be compensated again for those visits:

- [redacted] after the completion of Visit C1 – Lead placement
- after the completion of each Visit C2, C3, C4 in-clinic visits
- after the completion of each Visit C5, C6, C7 telephone calls

[redacted]

[redacted] Subjects will also be compensated [redacted] for unscheduled visits or follow-up visits related to ADEs.

6.0 INFORMED CONSENT PROCESS

In accordance with applicable regulations, 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.

7.0 DATA COLLECTION AND MANAGEMENT

7.1. Data Collection

For this study, an Electronic Data Capture (EDC) system which utilizes electronic CRFs (eCRFs) will be used. A 21 CFR Part 11 compliant system will be selected for use which enables entry of study data into an Electronic Data Capture system by each participating clinical site or the subject directly. [redacted]

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

7.2. 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 HIPAA regulations will be followed.

7.3. Data Processing

All EDC study data and paper documentation will be monitored by SPR Therapeutics personnel (or their authorized representatives). Any missing or inconsistent data will be resolved via data queries.

7.4. Subject Screening and Identification Log

A subject screening log will be completed at the clinical site for all subjects who were considered for the study. Those individuals who are excluded will be listed along with the reason for exclusion. Any subject who signs an Informed Consent and does not proceed with procedures associated with treatment or fails to meet eligibility (*e.g.*, baseline diary back pain score < 4) will be considered a screen failure. The Subject Identification log will be completed for subjects enrolled in the study.

7.5. Subject Numbering

Screened and consented consecutive subjects will be given a unique Subject ID number. Subjects who sign consent and do not meet all study eligibility criteria will be considered screen failures and not count against the number of enrolled subjects. Subjects who are randomized at Visit 2 will be counted as enrolled. A number will be assigned consecutively to each subject at each clinical site. A master list linking the subjects to the unique "Subject ID" numbers will be kept by the study staff in a secure location.

8.0 DATA ANALYSIS AND STATISTICAL METHODS

All primary and secondary outcome data will be analyzed and reported. Each clinical site or individual clinician may be analyzed separately. The study objective is to compare the safety and effectiveness of percutaneous PNS for the treatment of low back pain to standard interventional management. The study will determine if the treatment effect of percutaneous PNS is equivalent (*i.e.,* statistically non-inferior), and if so, if it is superior, to standard treatment with standard interventional management.

8.1. Plan to maximize subject retention and minimize loss of data

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

Prior experience indicates a potential cause of data loss is when a lead is dislodged or removed before scheduled end of PNS therapy (60 days). [redacted] Additional instructions have been provided regarding bandaging to the subjects to minimize the chance of accidental lead dislodgement.

Subject withdrawal from the study is a potential source of data loss. Study investigators and staff will be trained to have clear discussions with subjects considering withdrawing from the study. During the discussions, subjects will be reminded that they may withdraw from the study at any time and investigators will determine if any burdens of continuing in the study can be eased to enable participation at a level that is more amenable to the subject. For example, if subjects indicate a lack of interest in continued participation, they can be offered an opportunity to provide only the most essential and easily collectable data (e.g., recall pain scores and AE questions regarding their safety). To further reduce burden associated with time and travel to the clinical site, subjects can be provided with the option to complete AE questions, surveys, or diaries over the phone or return these via other methods (e.g., a preaddressed, postage-paid envelope, email, ePro, etc).

Subjects in either group may continue to participate in the study visits independent of their successful completion of diagnostic procedures and/or standard interventional management. These subjects may be offered the option to continue with the study and provide only the most essential and easily collectable data (including the option of switching to all telephone calls and completing the most important visits). Subjects also have the option to receive SOC LBP treatments from their regular, outside medical providers (i.e., not exclusively from the study site). If so, these subjects will continue to be followed by the site for research only visits/calls. Alternative options may be utilized to minimize data loss in subjects.

Subjects may elect not to undergo a diagnostic procedure and/or treatment (*e.g.,* subject elects to continue their usual care for back pain) but are still willing to remain in the study. In this event, if the subject has not undergone a diagnostic procedure by the end of the Visit 3 window, they will progress directly to Visit 4 (i.e., Visit 3 will be marked as "missed" and Visit 4 will be completed via phone). Regardless of the mode of participation, subjects

who continue participation through 12 months after "Start of Treatment" (completion of Visit 16) will be eligible for crossover.

Subjects are offered compensation for each visit as it is completed, including unscheduled visits, even if they do not complete all the visits. This compensation is intended to cover costs associated with taking the time to participate in the study. [redacted]

A potential source of data loss is the failure of the subjects to return their completed diaries. Thus, subjects may receive reminder calls from the clinical study staff before certain visits to remind them to bring their completed diaries with them to the visit. For long-term follow up visits, subjects may complete a diary after a visit and return via mail/email if the original diary for that visit was lost or was not completed. Diaries may also be completed electronically.

If a subject is unable to return any follow-up diary, the data may be replaced using the one-week recall data (question #3 or #5 of the validated BPI-SF). If the subject later returns the diary, the diary data will be used over the one-week recall data. If a subject is unable to return to the clinic for a visit, options to collect the most important assessments (e.g., pain intensity, ODI) and data (e.g., LBP treatment use, adverse events, etc.) will be made available to the subject (e.g., assessment of surveys and visit questions via phone or video call, remote completion of surveys via mail, email, ePro, etc.). These options will mitigate the problem of missing data and minimize the need to impute scores. Scores will only be imputed if recall (or remotely collected) data are unavailable and cannot be obtained.

Additional steps will be taken as necessary to maintain a high level of subject participation and follow up. For example, if a subject relocates during the study, arrangements will be made either to provide transportation for the subject to attend their visits at the clinical site, or to allow the subject to receive the necessary follow up at a medical center in closer proximity to their new location and a referring physician located near the subject will conduct the visit with the assistance of an investigator and/or a technical representative from SPR Therapeutics as needed. In the event of a local or national emergency (e.g., pandemic, natural disaster, safety concern), visits may be performed by phone if necessary. These rare instances should be reviewed and approved by the Sponsor prior to completion.

8.2. Safety Endpoint Analysis

All study-related adverse events will be documented, reported, and categorized.

9.0 STUDY TRAINING, MONITORING, AND DEVICE ACCOUNTABILITY PROCEDURES

9.1. Study Training

SPR Therapeutics or their designee will conduct a Site Initiation and Training Visit prior to initiation of the study. The purpose of this visit will be to develop a common

understanding of the clinical protocol, Case Report Forms (CRFs), study specific procedures, Investigator Responsibilities, and Good Clinical Practices (GCPs) among SPR and the Clinical Site team.

9.2. Study Monitoring

9.2.1 [redacted]

SPR Therapeutics or a designated qualified study monitor will monitor this study. Other appropriately qualified clinical monitors may also be involved in the monitoring of study sites. Monitoring visits to the Clinical Site will be conducted periodically, as determined by the rate of subject enrollment, during the study to ensure that the most currently approved version of the 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 Clinical 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.

9.2.2 [redacted]

9.3. Device Accountability

Devices will be used from the site's commercially available stock. Site will report all device usage to SPR for device accountability and device tracking purposes.

9.3.1 Returning used devices to SPR Therapeutics

If a device needs to be returned to SPR, the site will contact SPR for instructions prior to returning any devices.

9.4. Independent Clinical Events Reviewer

An independent Clinical Events Reviewer will be utilized for this study to adjudicate all adverse events (AEs). AE information, including group assignment, will be provided to the Reviewer. In these situations, the adjudication by the Clinical Events Reviewer will be the final determination.

9.5. Designation of the Study Monitor

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

SPR Therapeutics, Inc.
22901 Millcreek Boulevard, Suite 500
Cleveland, OH 44122
Phone: 216-378-9108
Fax: 216-674-2303

9.6. Adverse Events

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

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

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

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

Study Personnel will report any UADE by telephone and email to SPR Therapeutics within 24 hours of learning of the event. The event is reported by telephone and a completed AE form will be emailed to SPR Therapeutics staff as indicated in **Table 2.** Follow-up information and the complete UADE report will be forwarded to SPR Therapeutics as the event continues and/or resolves.

During training, the clinical site will be provided with detailed instructions to report ADEs and UADEs. Sponsor contact information for reports of Unanticipated Adverse Device Events is provided in **Table 2.**

Table 2: Unanticipated Adverse Device Event Sponsor Contact Information

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

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

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

10.0 RISK BENEFIT ANALYSIS

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

10.1. Potential Benefits

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

This research may benefit future patients with chronic low back pain.

10.2. Known and Anticipated Risks

The known and anticipated risks summarized below are described as expected to be either common (occurring about 10% of the time), uncommon (occurring about 1-10% of the time), or rare (occurring less than 1% of the time). Group #2 subjects will be receiving

therapies that they would normally receive if they were not participating in the study, only the risks that are specific to the study are detailed below.

The following risks apply to the subjects who receive PNS:

[redacted] **Risks associated with insertion of the needle introducer for lead placement**

[redacted]

[redacted]

Risk of skin irritation, infection, or inflammation at the lead exit sites

[redacted]

[redacted]

Risk of the percutaneous lead breaking beneath the skin

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] **Risk of skin irritation under the pad or bandages**

[redacted]

[redacted]

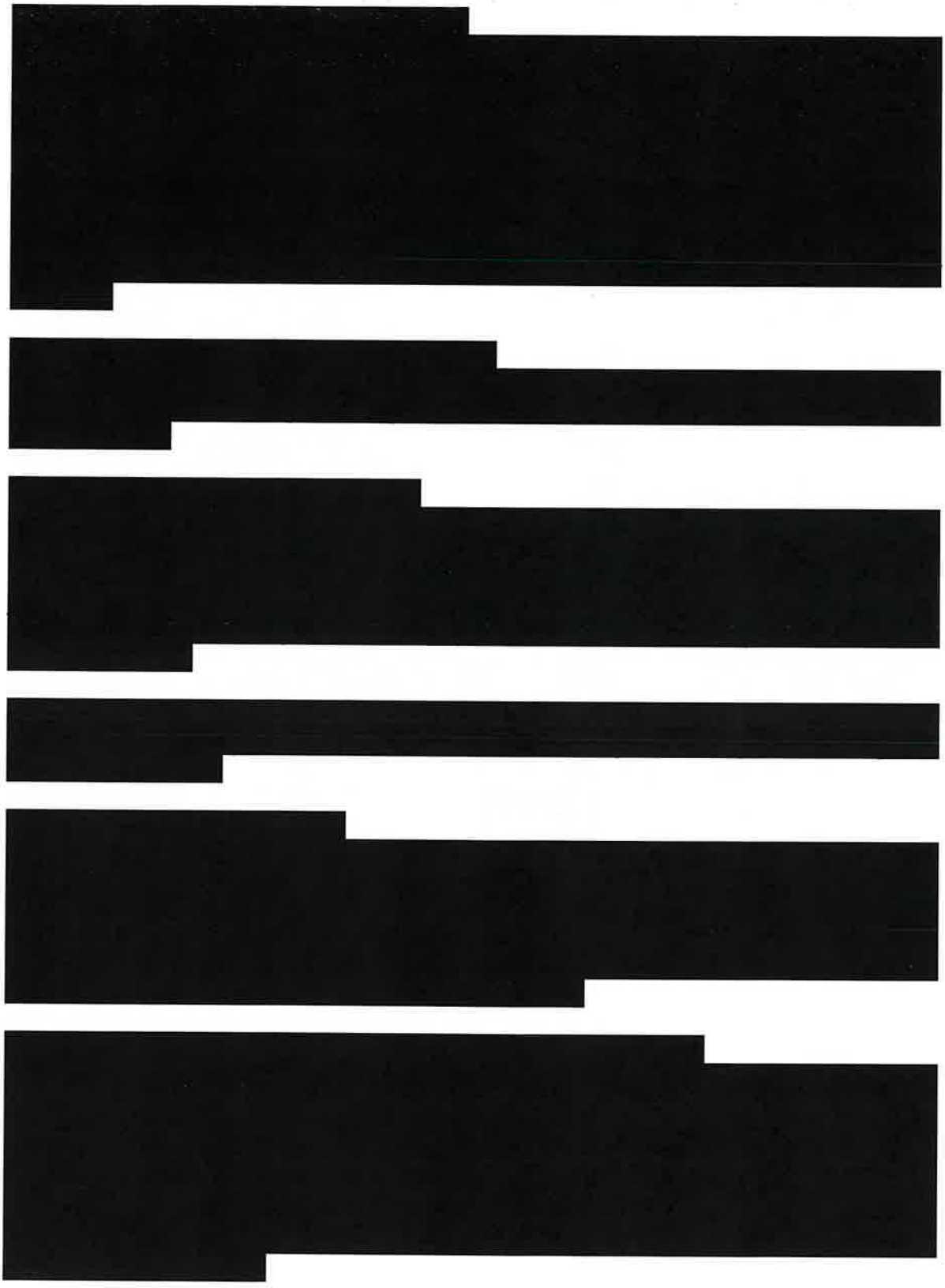
[redacted]

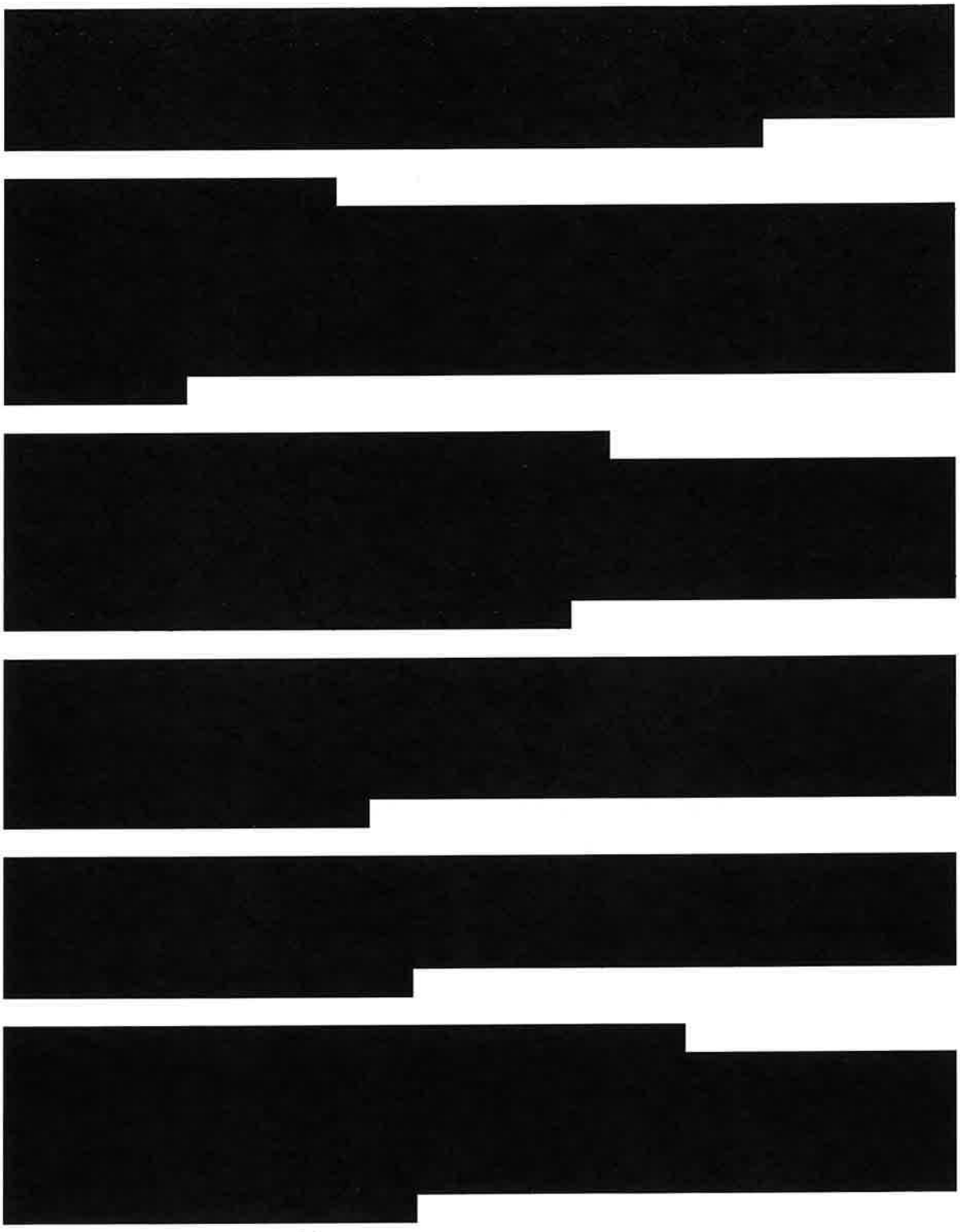
Risk of discomfort or increased pain

[redacted]

[redacted]

[redacted]





[redacted]

Risks associated with medial branch block

[redacted]

Risk of loss of confidentiality

[redacted]

10.2.1. Risk Analysis

[redacted] all efforts will be made to mitigate each potential risk associated with the use of the system. Despite all attempts to mitigate the risks associated with the use of the system, it is possible that these events and other unanticipated events may occur. Though subjects may experience no benefit to participating in this study, the knowledge gained from the results and the application of that knowledge toward the future development of a stimulation system may benefit future patients and significantly improve the quality of life for patients suffering from chronic low back pain. The potential risks of participation in this study have been minimized such that they are unlikely to occur and/or

have non-serious consequences. The knowledge gained from the study and the potential for relief of pain justifies the minimal potential risk.

Alternative therapies are available for the treatment of chronic low back pain. These other therapies, including pain medication for relieving pain, steroid injections to reduce pain from inflammation, acupuncture, Botox injection, or exercise and physical therapy may be beneficial and may provide pain relief or may have their own disadvantages.

11.0 STUDY ADMINISTRATION

11.1. Record Retention

By signing the Investigator Agreement, the Investigator agrees to retain study-related documents in a secure location to which access can only be gained if required. Following study completion, the following documents will be archived: the study regulatory files containing all Essential documents, including signed Informed Consent forms, patient-related materials, and CRFs. The Investigator will be required to retain all records required by this study per their contract with the sponsor. The investigator must inform SPR Therapeutics if the location of the records changes or if there are any plans to destroy the records.

11.2. 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.

11.3. 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.

11.4. Investigator Qualifications/Responsibilities and Investigator Training

To participate in this study, the Investigator must sign the Investigator Agreement, which documents his responsibilities in the study. The Investigator will require training on this study plan and the device. These elements will be covered during an Investigator Training session and may be conducted during the Site Initiation Visit. The Investigator/Coordinator Training will include the following elements; however, the curriculum may be slightly modified as necessary:

- Study objectives
- Subject selection criteria
- Completion of CRFs
- Device Overview and Device Operation
- Reporting of Adverse Device Effects
- Good Clinical Practice Regulations

- Any other information that is deemed necessary to ensure that the clinical team is knowledgeable about the protocol, the Device, and the manner in which it will be used in this study.
- Device/lead placement training will also occur prior to the first lead placement.

11.5. Statements of Compliance

11.5.1. Declaration of Helsinki

This research study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

11.5.2. International and National Standards

This research study shall comply with any applicable federal (21 CRF Parts 11, 50, 56, 812) and international standards (ISO 14155) and ICH Good Clinical Practice Guidelines.

11.5.3. Institutional Review Boards

This research study shall not begin until the applicable approvals have been obtained from the governing Institutional Review Board (IRB) where the research will be conducted. Any additional requirements imposed by the governing regulatory authorities and/or IRB will be followed.

12.0 DEVIATIONS TO THE PROTOCOL

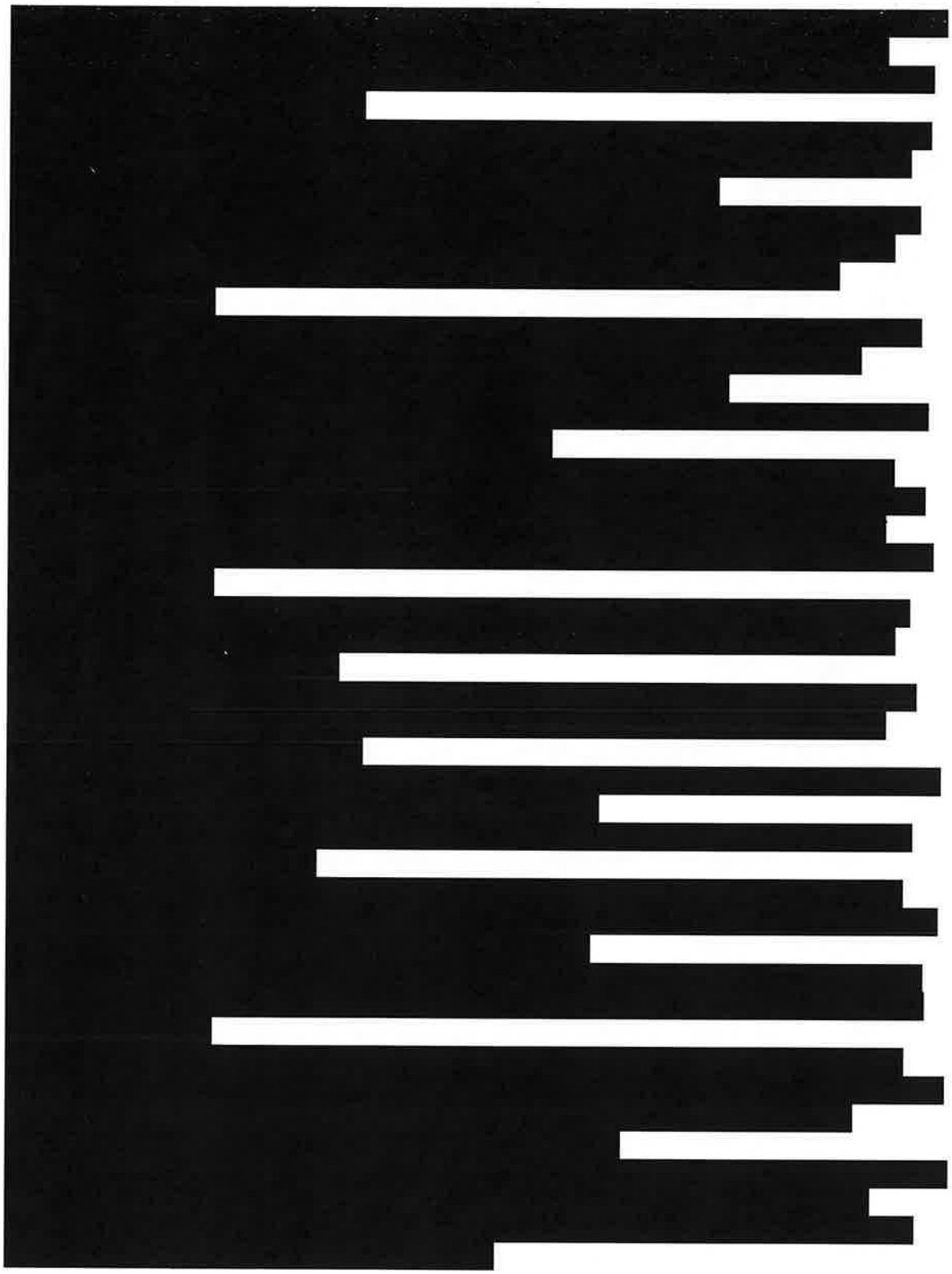
Protocol deviations are defined as an unplanned excursion from the protocol that is not implemented or intended as a systematic change, or any other unplanned instance(s) of protocol noncompliance.

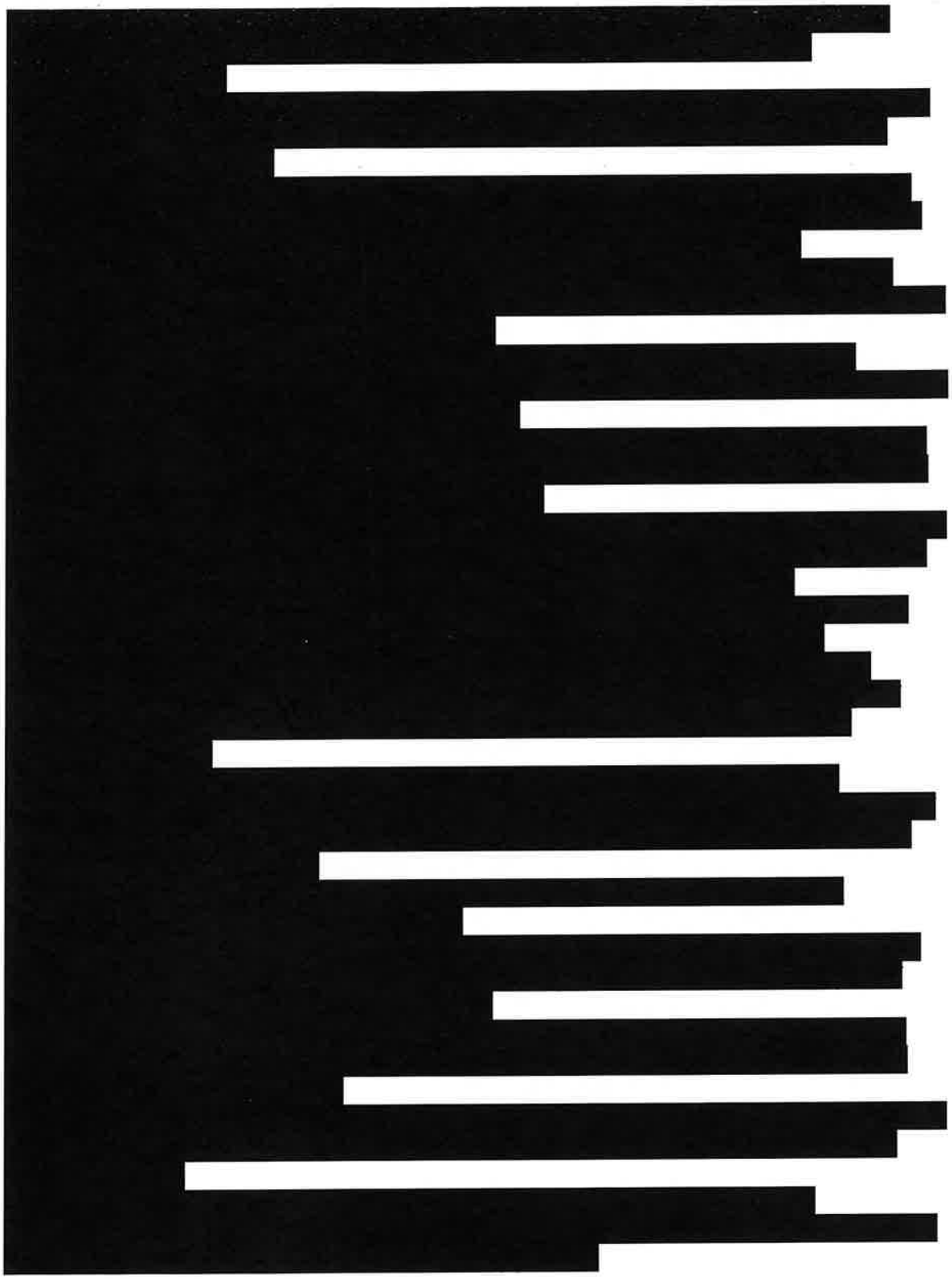
The Investigator must not deviate from the protocol, except when necessary to protect the life or physical well-being of the subject. Whenever possible, the Investigator will obtain the permission in advance for protocol violations from SPR Therapeutics and the governing IRB (in accordance with its reporting requirements). Deviations will be recorded on a protocol deviation log and reviewed by the study monitor to address any needs for corrective and preventive action. Deviations will also be reported as part of the final study report.

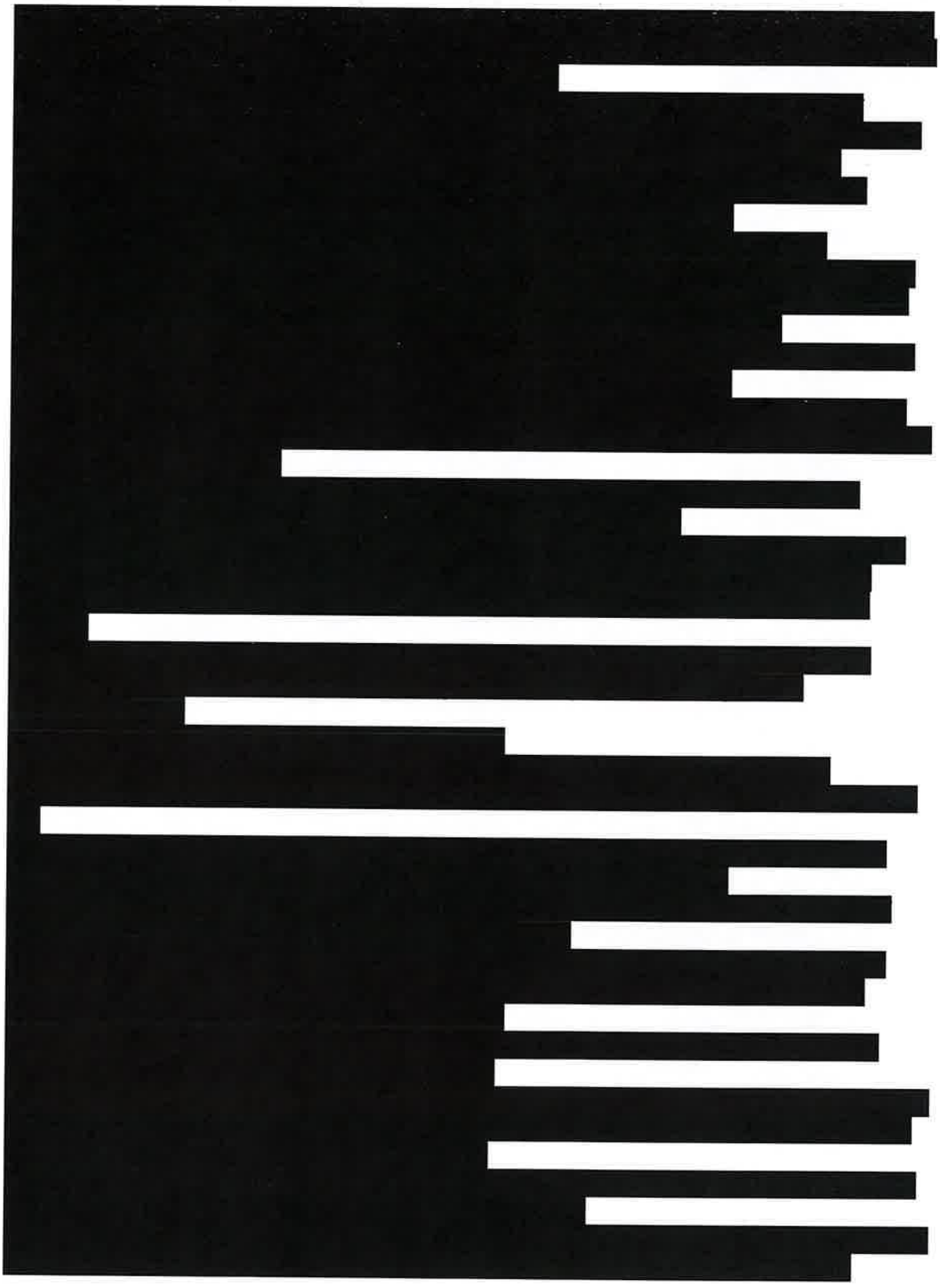
13.0 [redacted]

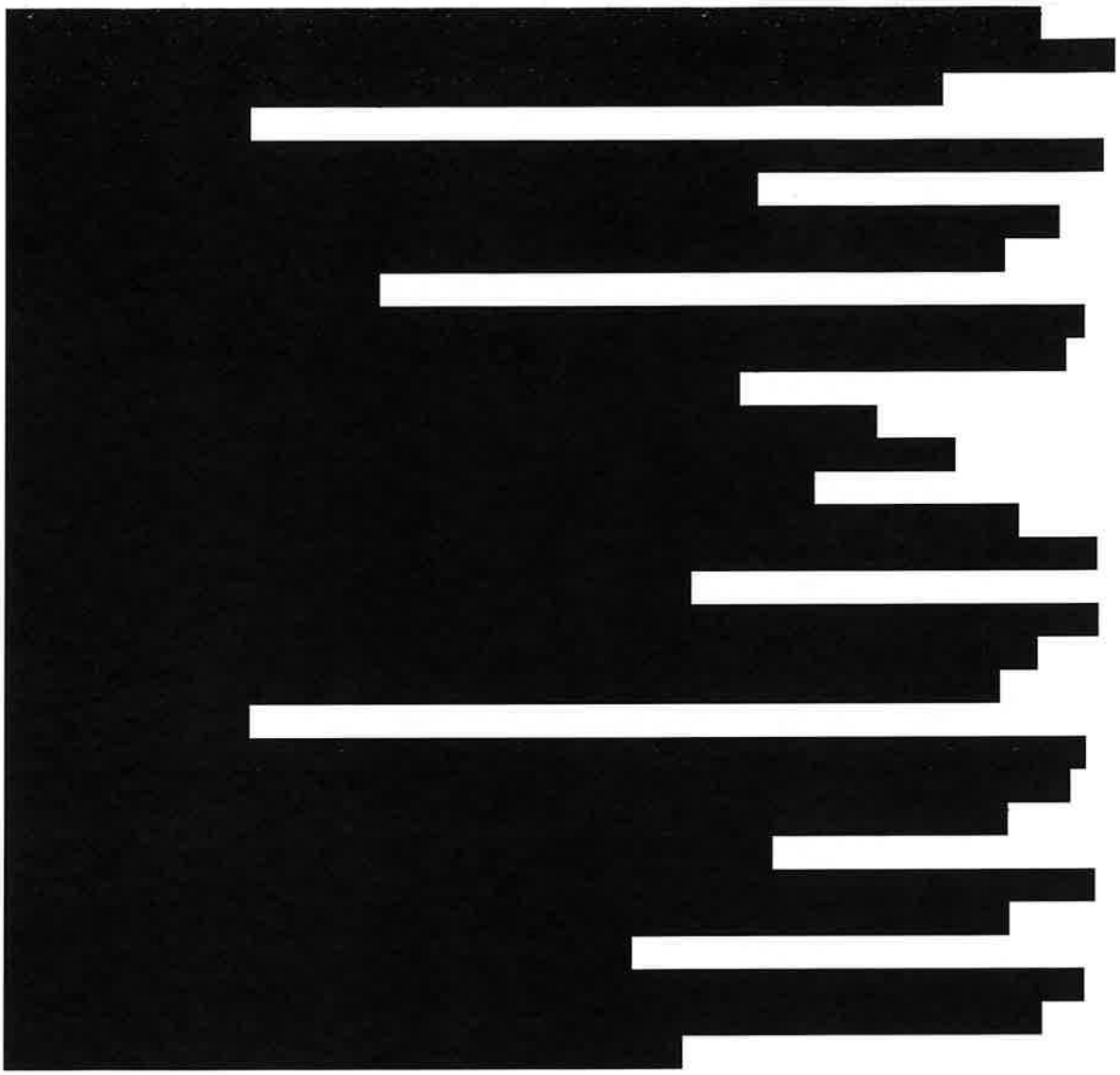
14.0

[redacted]









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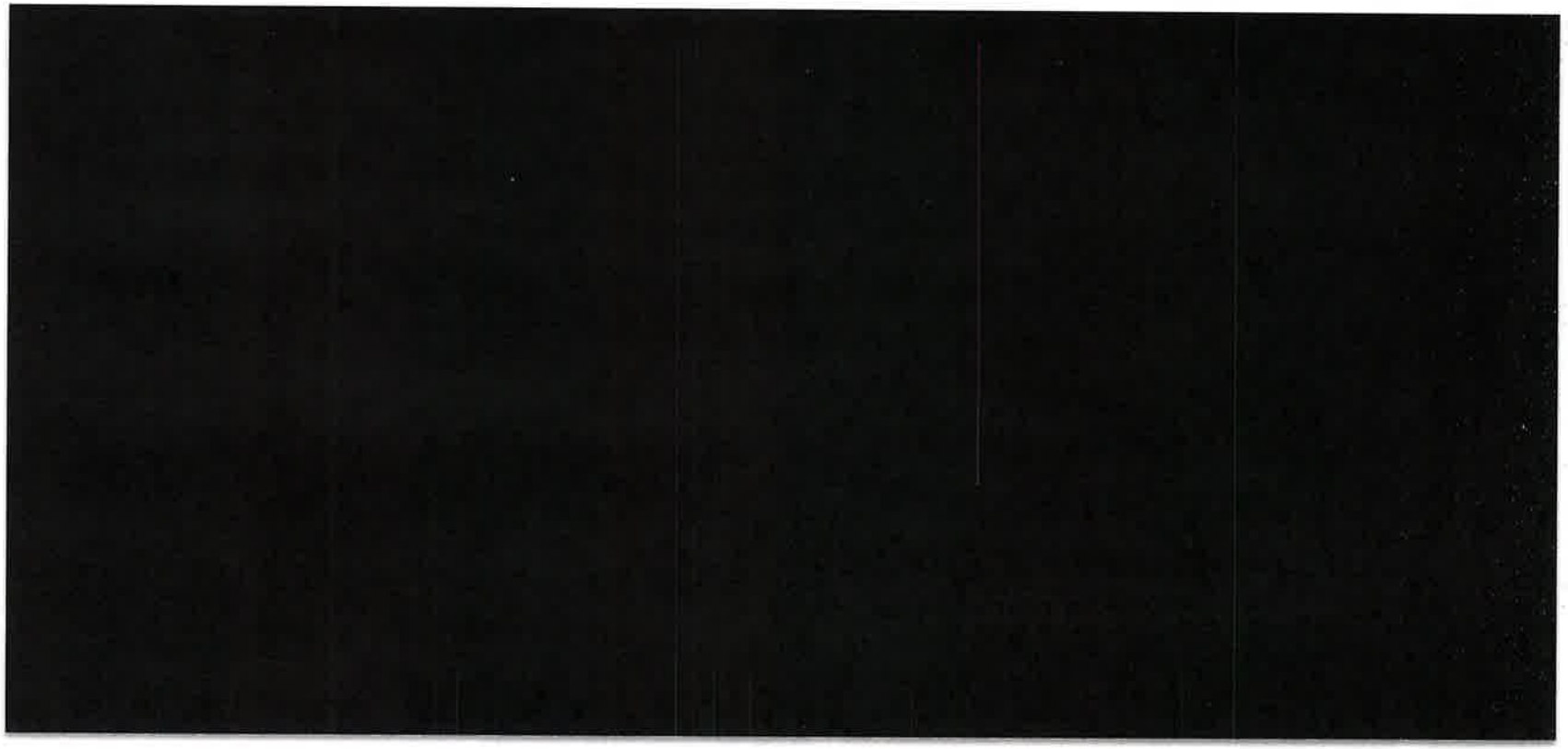

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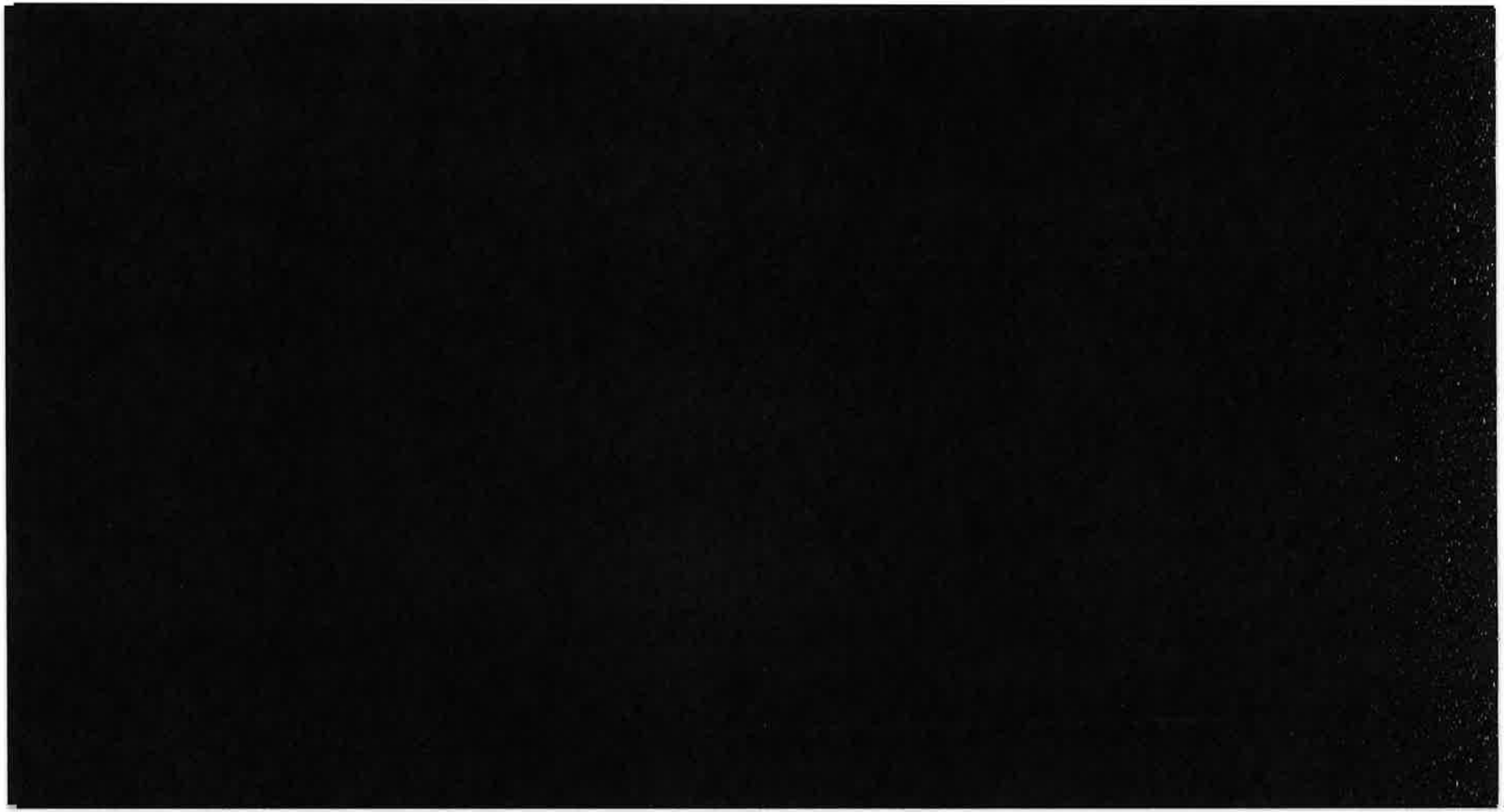

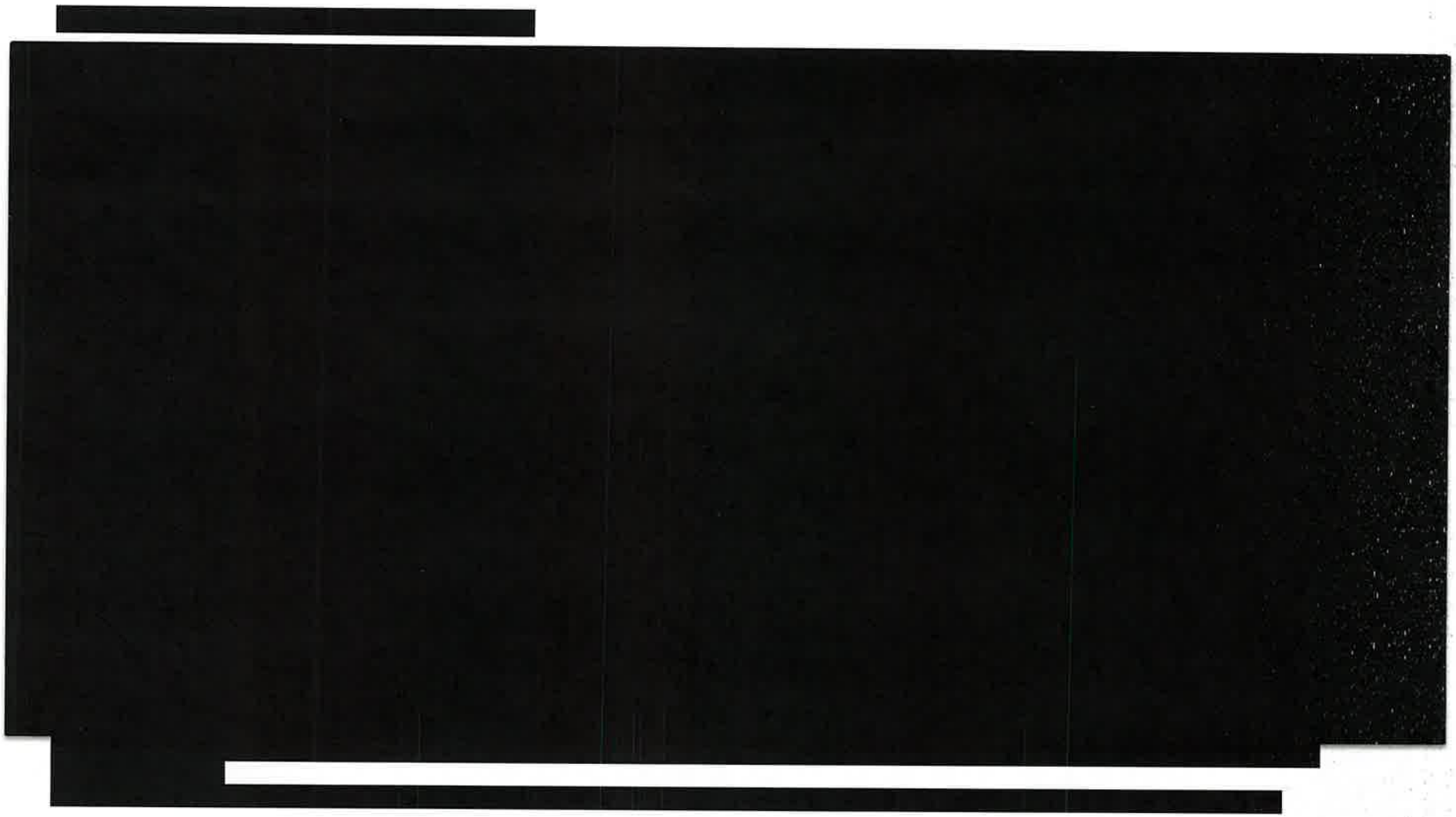

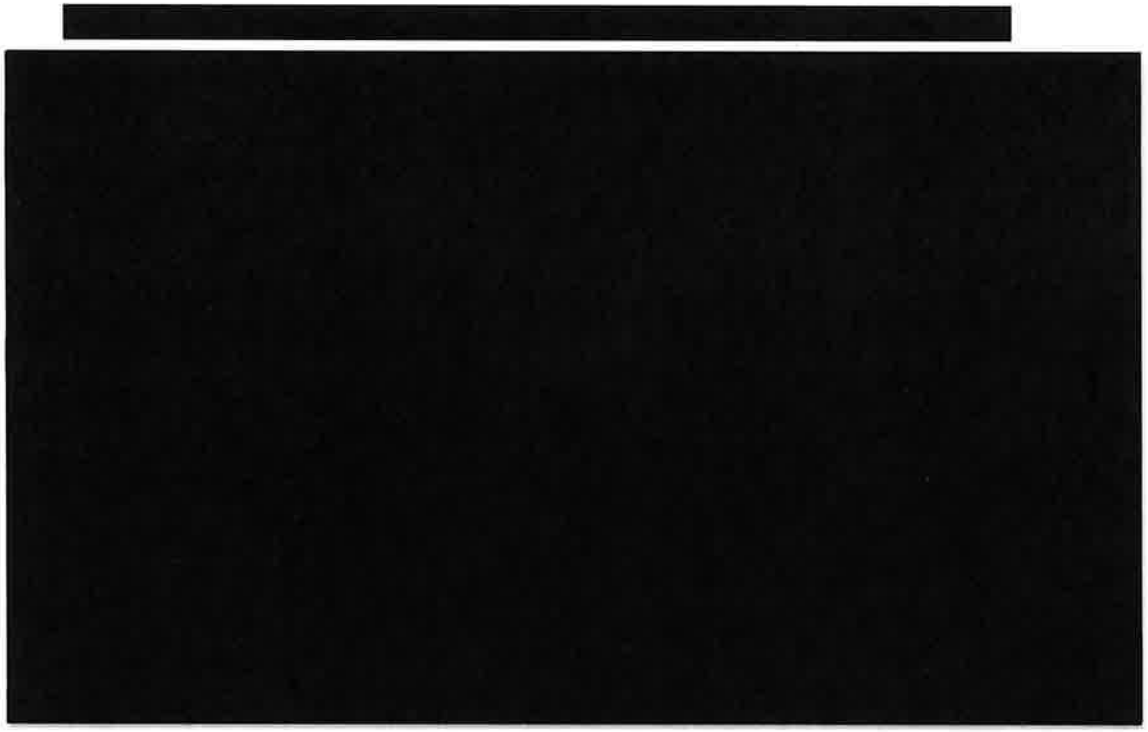

Appendix C. Subject Participation Flow Chart for Visits 1-18*