Official Title:
Treatment of Post-Operative Pain Following Orthopedic Surgery with SPRINT® Peripheral Nerve Stimulation (PNS) System in a Randomized, Double-Blinded, Placebo-Controlled Trial

NCT#: 04341948

Date: 06 June 2022

Treatment of Post-Operative Pain Following Orthopedic Surgery with SPRINT® Peripheral Nerve Stimulation (PNS) System in a Randomized, Double-Blinded, Placebo-Controlled Trial

Sponsor:	SPR™ Therapeutics, Inc. 22901 Millcreek Boulevard Suite 500 Cleveland, OH 44122
Study Device:	SPRINT® PNS System
FDA Clearance for SPRINT ® PNS System:	K181422; K202660; K211801
Initial Date and Version:	[redacted]
Amendment Dates/Versions:	[redacted]
	[redacted]
	[redacted]
	[redacted]
	June 06, 2022 [redacted]

Protocol Synopsis

Title	Treatment of Post-Operative Pain Following Orthopedic Surgery with SPRINT® Peripheral Nerve Stimulation (PNS) System in a Randomized, Double-Blinded, Placebo-Controlled Trial
Device (510k Cleared)	The SPRINT® Peripheral Nerve Stimulation (PNS) System
Study Design	Randomized, Double-Blinded, Placebo-Controlled, Multicenter Post Market Study
Primary Study Objective	The study objective is to gather data on the use of the PNS therapy for the treatment of postoperative pain following orthopedic surgery. The study will compare the responses of two groups.
Study Plan	Individuals must have persistent, average pain score of ≥ [redacted] out of 10 following surgery to qualify Individuals who have undergone primary, unilateral or bilateral total knee replacement (TKR)/revision (PKR) and report [redacted] unilateral postoperative pain (≥ [redacted] on an 11-point numerical rating scale on the Brief Pain Inventory Short Form (BPI-SF Question #5)) will be considered for enrollment into the study. After informed consent is obtained, potential subjects will be evaluated for general eligibility. The individuals who satisfy the preliminary criteria will be asked to complete an assessment of baseline pain to determine if their postoperative pain is persistent. Percutaneous leads will be placed to target the nerves [redacted] innervating the region of pain Qualifying subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control). In all subjects, leads will be placed [redacted] All subjects will be instructed to use the SPRINT Stimulator [redacted] during the 8-week treatment period. In Group #1, the system will deliver active electrical stimulation, while in Group #2, the system will deliver sham (placebo) stimulation during the 8-week treatment period. [redacted] After lead removal, Group #1 subjects will be followed for 12 months from the start of treatment (SOT). Group #2 will be given the option of crossing over Following the completion of a follow-up visit [redacted] Group #2 subjects will be given the option of crossing over to receive active stimulation. If subjects do not choose to receive active stimulation, they will be discharged from the study. If subjects choose to receive active stimulation, leads will again be placed [redacted]

[redacted] and the system will deliver active electrical stimulation [redacted] After lead removal, the subjects will be followed for 12 months from the start of the crossover stimulation treatment.

The schedule of study visits and assessments is [redacted] with scheduled clinic visits at baseline [redacted] Subjects will additionally receive scheduled telephone calls [redacted]

Daily medications affecting pain will be permitted at levels established during baseline.

All subjects will be permitted to continue use of all baseline medications affecting pain throughout the study; [redacted] To be eligible for lead placement, individuals cannot have added any new medications affecting pain, including as-needed (PRN) medications, within the 4 weeks prior [redacted] Consistent with clinical practice for clinical trials, subjects will be permitted to use additional over-the-counter (OTC) supplemental medications throughout the study for breakthrough knee pain or other pain (*e.g.,* headache, backache, toothache).

Each site will designate a study team member to serve as the blinded evaluator, who will not know the group to which each subject is randomly assigned. The subject and the blinded evaluator will be blinded to the study assignment. Each site will also designate study staff that will remain unblinded. The unblinded staff will be responsible for actions that the blinded evaluator cannot perform, [redacted]

Sites (N)	Up to 15 sites
Subjects (N)	Up to [redacted] subjects [redacted] will be randomized
Inclusion Criteria *(assessed at Eligibility Visit 1)*	• At least 21 years old • Underwent a 1. Primary total knee replacement (TKR), 2. Secondary/revision TKR or 3. Partial/unicompartmental knee replacement (PKR) • Knee pain directly resulting from knee replacement surgery in affected knee ≥ [redacted] on a scale of 0-10 (BPI-SF, question #5) • Able to understand and provide written consent • Able to comply with all study requirements (e.g., if needed, has a caregiver to assist)
Exclusion Criteria *(assessed at Eligibility Visit 1)*	• Change of prescribed medications affecting knee pain within the past 4 weeks [redacted] • Current high opioid use (i.e., [redacted] mg oral MED in a single day) • If subject reports any opioid use within the past 4 weeks [redacted] subject must not have used opioids daily for the month preceding knee replacement [redacted] • If subject reports any opioid use within the past 4 weeks [redacted] subject must not have used [redacted] mg oral MED on any day during the month preceding knee replacement [redacted] • Body Mass Index (BMI) > 40 kg/m^2 • Compromised immune system based on medical history [redacted] or other conditions that places the subject at increased risk in the opinion of the investigator • History of valvular heart disease • 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. • History of bleeding disorder (e.g., hemophilia) or subjects with active anticoagulation whose use or temporary modification for the lead placement procedure places the subject at increased risk in the opinion of the investigator. • Confounding conditions [redacted] • Diagnosis of Diabetes Mellitus Types I or II

	• History of nerve damage in the affected leg [redacted] • Confirmed tape or adhesive allergy. • Contraindications to the proposed anesthetic protocol [redacted] • Any other condition that may interfere with the ability to participate in a clinical trial [redacted] as determined by the Investigator • Prisoners, minors, or individuals that report to investigators (e.g., students, employees) • History of substance abuse [redacted] • Potential secondary gain issues related to knee pain (*e.g.*, pending claims or receiving disability) • Botulinum toxin injection [redacted] in the affected limb • Steroid injection [redacted] in the affected limb • Subject has participated in any drug or device trial in the past 30 days • Subject has participated in previous [redacted] SPR Therapeutics sponsored study
Additional Inclusion Criteria (assessed before randomization)	• [redacted] baseline pain: Average pain intensity score of ≥[redacted] (determined by calculating the mean "average pain" collected in a 7-day diary, using Question #5 on the BPI-SF; mean score must be ≥[redacted]). • Persistent baseline pain: Rating of average pain intensity over past week (BPI-5) remains persistent for two consecutive weeks and is ≥[redacted]. [redacted]
Additional Exclusion Criteria (assessed before PNS)	• Pregnant (either urine dipstick or serum in females of reproductive potential)
Primary Safety Endpoint	Occurrence and type of study-related adverse events
Primary Clinical Endpoint	*Pain Intensity:* All subjects will record daily pain scores for the affected leg in diaries using BPI-SF Question #5. The percent change in pain scores will be determined for each subject by taking the mean of the daily average pain intensity (BPI-SF Question #5) reported in the baseline diaries compared to the mean score reported over Weeks 5-8 of the treatment period (i.e. the average of all diary scores during this

	period). Data will be collected as described in the Schedule of Procedures (Appendix A). 
Secondary Endpoints	• Average pain (BPI-SF Question 5) • Pain Medication usage • Pain Catastrophizing Scale (PCS) • Patient Global Impression of Change (PGIC) • Pain Interference (BPI-9) • Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) • Six Minute Walk Test (6MWT)
Exploratory Analyses	 •

Table of Contents

1.0 General Information

1.1 Title of the Investigation

Treatment of Post-Operative Pain Following Orthopedic Surgery with SPRINT® Peripheral Nerve Stimulation (PNS) System in a Randomized, Double-Blinded, Placebo-Controlled Trial

1.2 Sponsor Name and Address

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

1.3 Name of the Device

The SPRINT® Peripheral Nerve Stimulation (PNS) System

1.4 Indication for Use

The SPRINT PNS System is 510(k) cleared with the following Indication for Use.

The SPRINT Peripheral Nerve Stimulation (PNS) System is indicated for up to 60 days for:

- Symptomatic relief of chronic, intractable pain, post-surgical and post-traumatic acute pain;
- Symptomatic relief of post-traumatic pain;
- Symptomatic relief of post-operative pain.

The SPRINT PNS System is not intended to treat pain in the region innervated by the cranial and facial nerves.

1.5 Study Objective

The objective of this study is to gather data on the use of the PNS therapy for the treatment of postoperative pain following orthopedic surgery. The study will compare the responses to active stimulation vs. sham stimulation. [redacted]

[redacted]

1.6 Funding

The proposed study is funded by the sponsor and supported in part by the Department of Defense (DoD) U.S. Army Medical Research and Materiel Command, Congressionally Directed Medical Research Programs, Peer Reviewed Orthopedic Research Program-Clinical Trial Award W81XWH-17-PRORP-CTA. The contract number is W81XWH-18-1-0799.

2.0 Background and Justification for the Design of the Clinical Investigation

2.1 Postoperative pain following orthopedic surgery is a substantial medical problem

Postoperative pain following orthopedic surgeries such as bone fracture repair (*e.g.,* open reduction internal fixation), amputation, limb salvage, and joint replacement (*e.g.,* knee replacement), is moderate to severe in up to 90% of patients, and acute postoperative pain if uncontrolled can become chronic pain and last for several months to years[1-25]. Postoperative pain is treated using opioids and other oral medications, which can result in misuse and debilitating side effects. The side effects of opioids (*e.g.,* sedation, dizziness, nausea, constipation, urinary retention, sleeping problems) often interfere with function, activities of daily living, and physical rehabilitation[7, 26-31]. Also, patients following orthopedic surgery often use opioids for several weeks following surgery: the median time to cessation of opioids is approximately 1-2 months, and approximately 30% of patients are still on opioids at 90 days following surgery[32-35]. Such long-term use of opioids increases the risks of dependence, use of illicit substances (*e.g.,* heroin), overdose, and death[30, 36, 37].

Following orthopedic surgery, pain is one of the primary sources of disability that limit return to normal function[38-40]. For example, when traumatic injury results in amputation, pain rather than the loss of the limb is frequently what most impacts function, preventing completion of simple daily activities, and correlating most negatively with return to employment[38, 41, 42]. In addition, pain inhibits rehabilitation, preventing optimal recovery and the restoration of physical function[43-46]. Poor functional outcomes following bone fracture repair surgery, amputation, limb salvage, and joint replacement can persist for ≥1 year following surgery in 25-50% of patients, resulting in high rates of medical separation from service in the military and failure to return to work[12, 47-56].

Electrical stimulation has been used successfully to treat chronic pain, avoiding many of the debilitating side effects associated with medications[57-60]. However, electrical stimulation is rarely used to treat postoperative pain because of major limitations of existing methods. Transcutaneous electrical nerve stimulation (TENS) is seldom successful in treating postoperative pain because the required stimulation intensities to activate the deep pain-relieving fibers[61, 62] can irritate the skin and activate cutaneous nerve endings, causing discomfort and/or pain[63-65]; and low (comfortable) intensities are ineffective[58, 66-75]. Traditional methods of stimulation can reduce chronic neuropathic pain but require invasive surgery for system implantation. Spinal cord stimulation and conventional methods of peripheral nerve stimulation can activate nerve fibers from both superficial and deep tissues of the regions of pain by stimulating spinal/peripheral nerves with implanted electrodes, avoiding the intolerable cutaneous discomfort of TENS. However, these fully implanted systems require invasive surgery to place the electrodes and the stimulator. As a result, they are highly unsuitable as a temporary therapy for patients who have recently undergone major surgery.

Percutaneous peripheral nerve stimulation (PNS) is a temporary, non-surgical, and minimally-invasive therapy that is designed to overcome the barriers associated with traditional neurostimulation modalities. In this therapy, a fine wire open-coil lead is placed percutaneously to target peripheral nerves that innervate the region of postoperative pain. Percutaneous PNS enables selective stimulation of pain-relieving fibers and avoids unwanted muscle contractions, muscle weakness, and reduced proprioception to facilitate physical rehabilitation and accelerate functional recovery. The therapy is delivered using percutaneous open-coil leads designed for up to 60 days of PNS with minimal risk of infection. [redacted]

Because the lead is placed percutaneously, the approach can activate target nerve fibers while avoiding cutaneous discomfort. Also, this approach does not require invasive surgery to implement and can be delivered quickly without specialized training.

The goal of this randomized-controlled trial is to gather data on the use of the SPRINT PNS therapy for the treatment of postoperative pain following orthopedic surgery.

2.2 Percutaneous PNS has been tested to treat pain in patients following orthopedic surgery in prior studies.

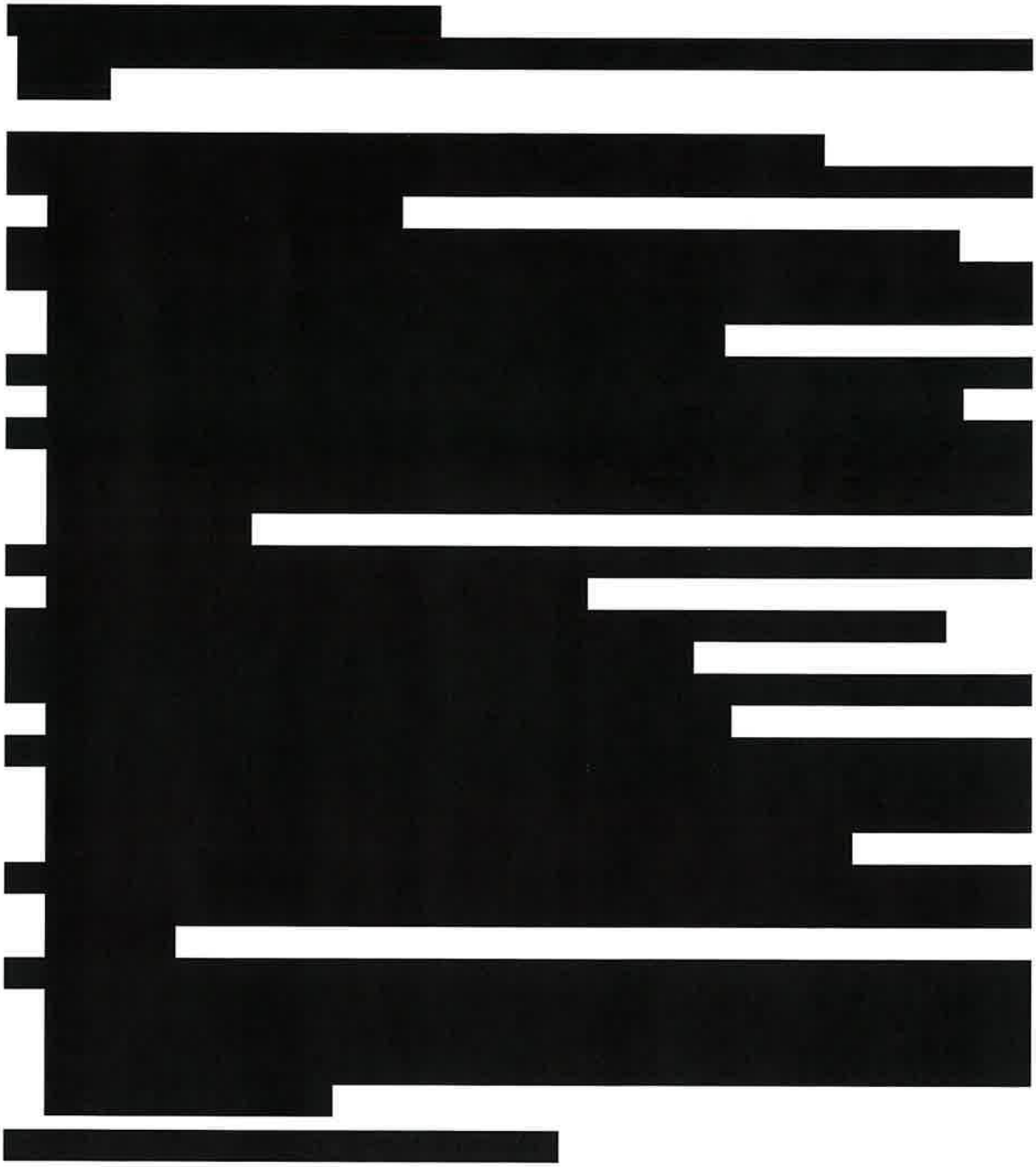
Ten subjects that had undergone TKR and were experiencing postoperative pain were enrolled. Of these subjects, 6 subjects were tested between postoperative day (POD) 6-14, and 4 subjects were tested between POD 40-100. The femoral and/or sciatic nerves were targeted using leads placed percutaneously, and the target nerve(s) were selected based on the location of pain (e.g., front or back of the knee). Leads targeting the femoral nerve were placed by inserting the introducer needle distal to the femoral crease and lateral to the femoral nerve, while leads targeting the sciatic nerve were placed using a trans-gluteal or popliteal approach. Stimulation amplitude and pulse duration were adjusted to provide comfortable sensations covering the regions of pain. Subjects rated their "Pain Right Now" on the Brief Pain Inventory Short Form (Question 6, BPI-6) with stimulation off and stimulation on. In 9 subjects (90%), pain at rest was reduced by a highly clinically significant amount (≥50%) with stimulation on (mean=1.4) compared to stimulation off (mean=5.4), with an average reduction of 75%. All leads were removed without discomfort or complication in a brief, out-patient procedure (*i.e.,* subjects did not take stimulation system home).

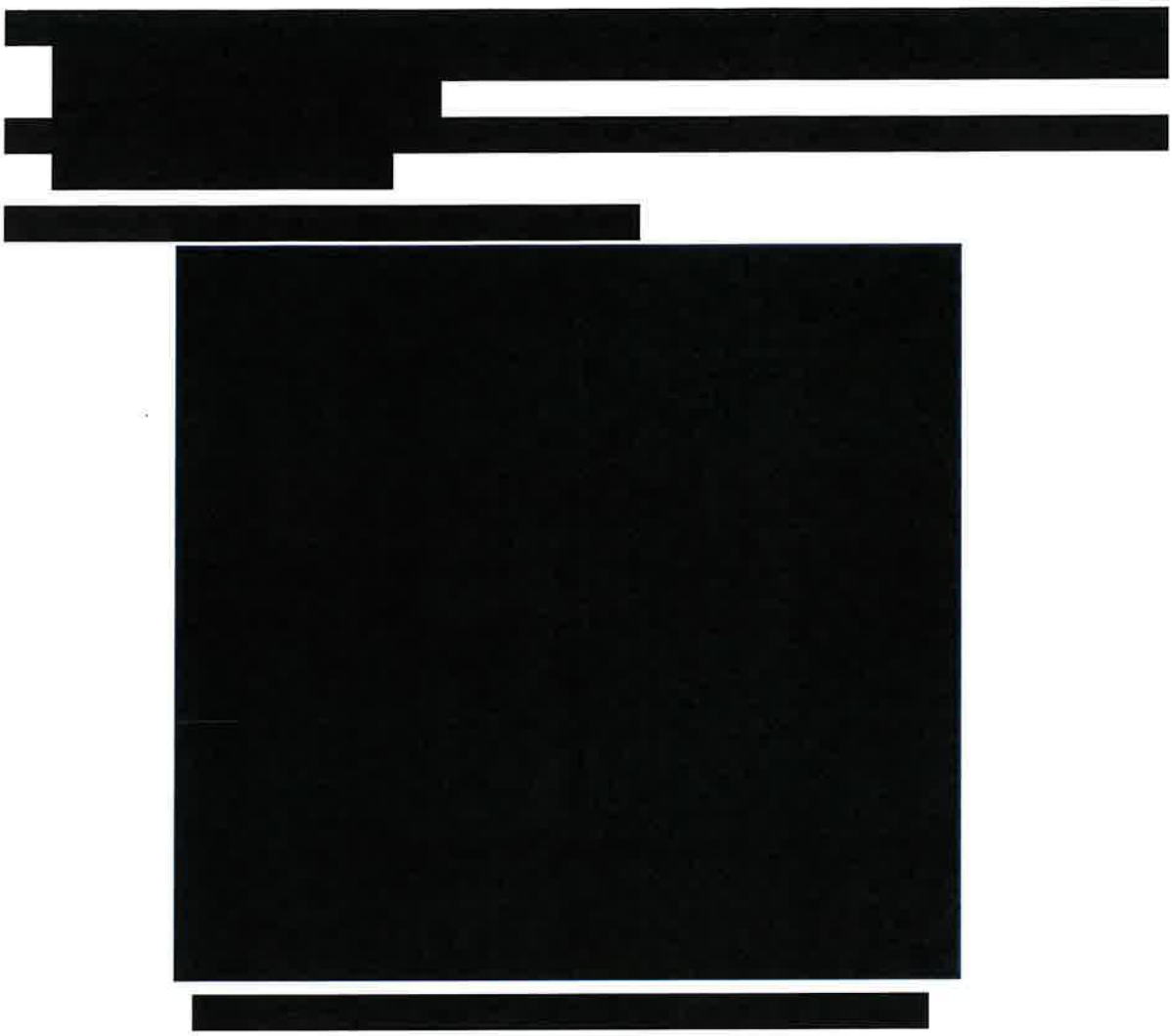
In another prospective case series study, subjects underwent lead placement 0-14 days prior to total knee replacement and received PNS following surgery for up to 6 weeks. Postoperatively at 1 month following surgery, the average pain over the previous week was mild and well-controlled (≤4/10) in 15/18 subjects (83%). Fourteen of 18 subjects (77%) had ceased opioid use by 62 days following surgery (*i.e.,* ≤25% of subjects still using opioids). At 3 months following surgery, 17 subjects (94%) had pain of ≤ 2/10, and 16 subjects (89%) had ceased opioid use. Overall, these results compared favorably to historical controls: persistent pain of ≥3 months after TKR is typically reported in 10-20% or more of patients[3, 8, 20, 24, 76, 77], and

25-40% of patients continue to use opioids at 90 days (3 months) after TKR[34, 78, 79].

3.0 Device Description

This study utilizes the commercially available SPRINT® PNS System. Electrical stimulation will be applied via [redacted] leads in the affected limb [redacted]





4.0 Study Design

4.1 General Overview

This study is a post-market randomized, double-blinded, placebo-controlled, multi-center study to gather post-market data on the use of peripheral nerve stimulation (PNS) therapy for the treatment of post-surgical pain following orthopedic surgery (*i.e.,* knee replacement). The treatment of post-surgical pain is included in the indication statement for the SPRINT® PNS System (K181422; K202660; K211801).

4.2 Study Population

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

4.2.1 Selection Criteria

Individuals who meet all of the inclusion and none of the exclusion criteria will be eligible to enroll in the study as subjects.

4.2.1.1 Inclusion Criteria

1. At least 21 years old
2. Underwent a
   a. Primary total knee replacement (TKR),
   b. Secondary/revision TKR or
   c. Partial/unicompartmental knee replacement (PKR)
3. Knee pain directly resulting from knee replacement surgery in affected knee ≥ [redacted] on a scale of 0-10 (BPI-SF, question #5)
4. Able to understand and provide written consent
5. Able to comply with all study requirements (*e.g.,* if needed, has a caregiver to assist)

4.2.1.2 Additional inclusion criteria (assessed prior to randomization)

1. [redacted] baseline pain: Average pain intensity score of ≥[redacted] (determined by calculating the average pain collected in a 7-day diary, using Question #5 on the BPI-SF)
2. Persistent pain following a knee replacement as assessed using weekly recall average pain intensity scores.

[redacted]

4.2.1.3 Exclusion Criteria

1. Change of prescribed medications affecting knee pain within the past 4 weeks [redacted]
2. Current high opioid use (i.e., [redacted] mg oral MED in a single day)
3. If subject reports any opioid use within the past 4 weeks [redacted] subject must not have used opioids daily for the month preceding knee replacement [redacted]
4. If subject reports any opioid use within the past 4 weeks [redacted] subject must not have used [redacted] mg oral

MED on any day during the month preceding knee replacement [redacted]

5. Body Mass Index (BMI) > 40 kg/m^2
6. Compromised immune system based on medical history [redacted] or other conditions that places the subject at increased risk in the opinion of the investigator
7. History of valvular heart disease
8. Deep brain stimulation (DBS), an implanted active cardiac implant, or any other implantable neurostimulator whose stimulus current pathway may overlap the SPRINT Stimulator's current pathway.
9. History of bleeding disorder (e.g., hemophilia) or subjects with active anticoagulation whose use or temporary modification for the lead placement procedure places the subject at increased risk in the opinion of the investigator.
10. Confounding conditions [redacted]
11. Diagnosis of Diabetes Mellitus Types I or II
12. History of nerve damage in the affected leg [redacted]
13. Confirmed tape or adhesive allergy
14. Contraindications to the proposed anesthetic protocol [redacted]
15. Any other condition that may interfere with ability to participate in a clinical trial [redacted] as determined by the Investigator
16. Prisoners, minors, or individuals that report to investigators (e.g., students, employees)
17. History of substance abuse [redacted]
18. Potential secondary gain issues related to knee pain (*e.g.,* pending claims or receiving disability)
19. Botulinum toxin injection [redacted] in the affected limb
20. Steroid injection [redacted] in the affected limb
21. Subject has participated in any drug or device trial in the past 30 days
22. Subject has participated in previous [redacted] SPR Therapeutic sponsored study

4.2.1.4 Additional exclusion criteria (assessed before lead placement)

1. Pregnant (either urine dipstick or serum in females of reproductive potential)

4.2.2 Subject Recruitment

Subjects with pain following a knee replacement surgery will be recruited by the investigators, following all HIPAA guidelines, to ascertain their level of interest and willingness to take part in this project. [redacted]

4.2.3 Duration of Subject Participation

Each subject's participation will last approximately 13 months (Group #1) or approximately 16 months (Group #2, if the subject chooses to crossover).

4.2.4 Duration of Study

[redacted]

4.2.5 Subject Disposition

Subjects that meet all eligibility criteria, including persistent average baseline pain scores of ≥ [redacted], will be enrolled in the study and randomized to either Group #1 or Group #2.

4.2.6 Vulnerable Population

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

4.3 Sample Size and Justification

Up to 15 sites will participate in this study. Up to [redacted] individuals will be enrolled as subjects and randomized to either Group #1 or Group #2. Subjects will be randomized at the start of Visit 2, after final eligibility is verified and before lead placement procedures begin. [redacted] Subjects who sign an informed

consent form and do not meet all study eligibility criteria will be considered screen failures and not count against the number of enrolled subjects.

4.4 Study Endpoints

Outcome measures will be collected from each subject in Group #1 (8 weeks of active stimulation) and Group #2 (8 weeks of sham stimulation) at Baseline and at specified follow-up visits [redacted] To support the study endpoints, the following outcome measures will be used:

1. Brief Pain Inventory, Short Form (BPI-SF)
2. Diary [redacted]
   - Average affected Knee Pain (rated using BPI Question 5)
   - Medication affecting pain, including reason for use
3. Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)
4. Patient Global Impression of Change (PGIC)
5. Pain Catastrophizing Scale (PCS)
6. 6 Minute Walk Test (6MWT)

[redacted]

4.4.1 Primary Endpoints

4.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be average post-operative pain, for primary TKR subjects only, in the affected knee from weeks 5-8 of the treatment period (in both Group #1 and Group #2) compared to baseline.

All subjects will record average knee pain scores (BPI-SF Question #5) for the affected knee in diaries [redacted] Subjects will record one pain score per day. For each subject, the 7-day baseline diary collection period will be used to calculate the mean of the "average pain." Each randomized subject must obtain ≥ 50% reduction during weeks 5-8 of the treatment period relative to the baseline score to be considered a success.

The primary endpoint of the study compares the proportion of successes of Group #1 (Treatment) relative to that of Group #2 (Control), [redacted]

4.4.1.2 Primary Safety Endpoint

The primary safety endpoint is the occurrence and type of study-related adverse events, also known as adverse device effects (ADEs). All ADEs that occur during the study will be documented and analyzed. [redacted]

[redacted]

4.4.2 Secondary Endpoints

Secondary endpoints will be collected to evaluate what effect, if any, the interventions have on each measure. Changes from baseline will be evaluated as secondary efficacy endpoints for the following outcome measures:

- Durability of the treatment effect on average pain intensity
- Average pain over the past week (BPI-5)
- Pain medication usage
- Pain Catastrophizing Scale (PCS)
- Patient Global Impression of Change (PGIC)
- Pain Interference (BPI-9)
- Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)
- 6 minute walk test (6MWT)

[redacted]

4.5 Amending the Protocol

This study will be carried out in accordance with this Study Protocol. SPR Therapeutics will prepare written amendments to revise the protocol, if necessary. Changes that are deemed administrative in nature, which do not require IRB approval (such as editorial changes for clarity or changes to contact information) may be made without any further approval. Documentation of the approval of the amendment will be maintained in the study regulatory files.

5.0 Study Procedures

The study procedures for this protocol are classified according to the following time periods: Baseline, Lead Placement, Treatment, and Follow-up. During the 8-week treatment period, Group #1 will receive active stimulation while Group #2 will receive sham stimulation. Following the [redacted] follow up visit, Group #2 will [redacted] choose to participate in an optional cross over and receive active stimulation or be

discharged from the study. Throughout the study, subjects will be asked to rate their average pain intensity over the last 24 hours in a daily diary and over the last week using the BPI-5. Medication usage and adverse events will be recorded.

[redacted]

5.1 Visit 1: Baseline

Individuals that have undergone a knee replacement surgery and report average post-surgical pain intensity over the past week rated as ≥ [redacted] (BPI-5) will be considered for enrollment into the study. Individuals will receive a detailed explanation of study-specific procedures as well as the risks and benefits of participating in the study. The individual will be asked to sign the approved study consent during this visit. If the individual agrees to participate by signing the consent form, general inclusion/exclusion criteria will be verified, and baseline information will be collected and recorded. Subject ID will be assigned.

[redacted]

[redacted]

The individuals who satisfy the preliminary criteria will be asked to:

1) complete a 7-day baseline diary to record their daily "average pain" intensity (Question #5 on the BPI-SF) and the use of medications affecting pain. [redacted]
2) rate their average pain intensity over the past week (BPI-5). [redacted]

[redacted]

5.2 Visit 2: Lead Placement and Testing (Day 0)

Following the baseline visit, individuals who qualify for lead placement (*i.e.*, meet the additional inclusion and exclusion criteria) will return to the clinic for placement of the percutaneous leads.

[redacted]

5.2.1 Randomization

Qualifying individuals will be randomized to either Group #1 (Treatment) or Group #2 (Control) using block randomization [redacted] Individuals will be blinded to their randomization assignment. [redacted] Subjects that are randomized will be considered enrolled in the study.

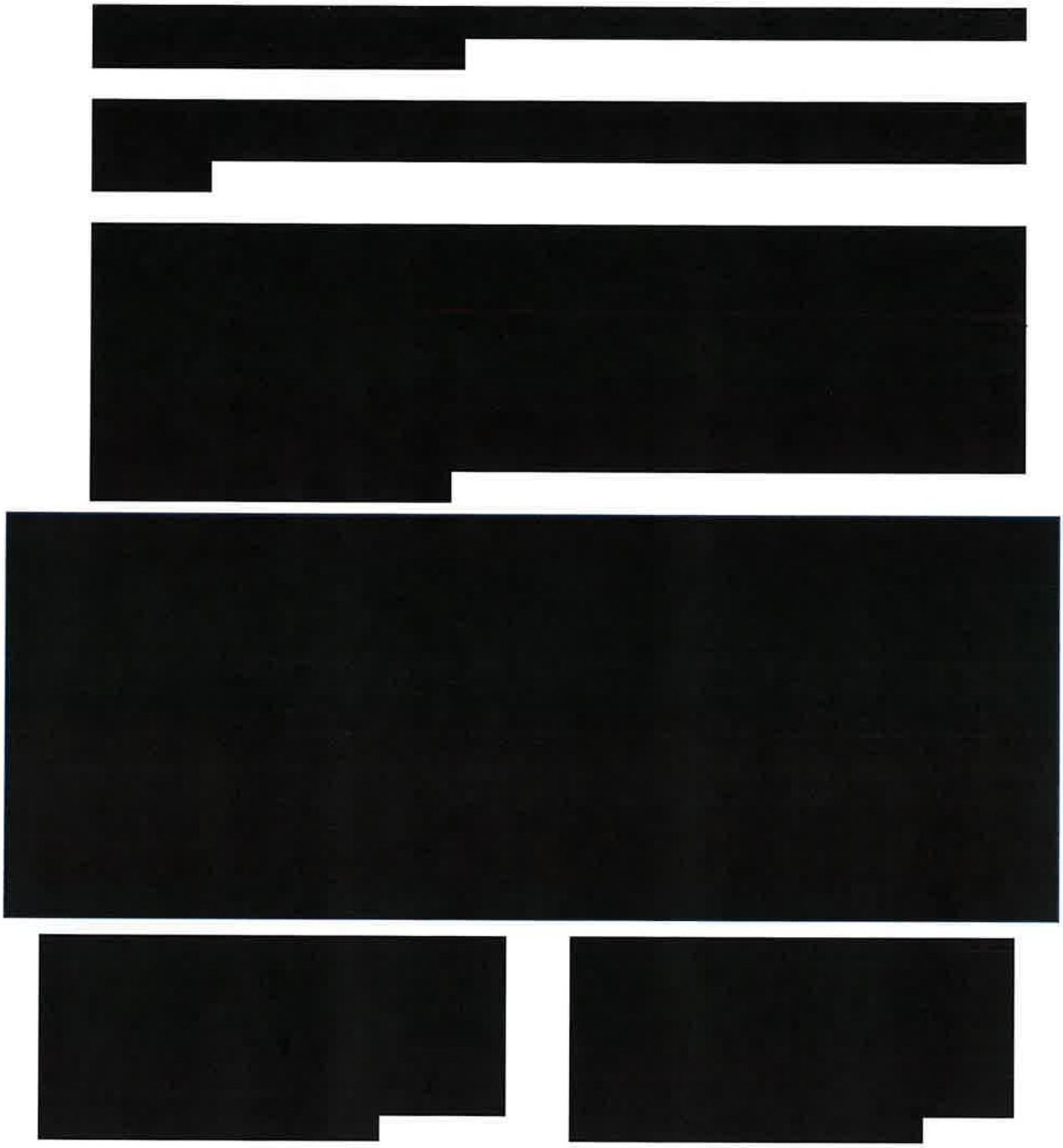
The group to which each subject is randomly assigned will remain concealed from the subject and the blinded evaluator until after Visit 11, but the randomization assignment will be made known to the unblinded study staff. The randomization assignment may be revealed early if considered medically necessary by the investigator.

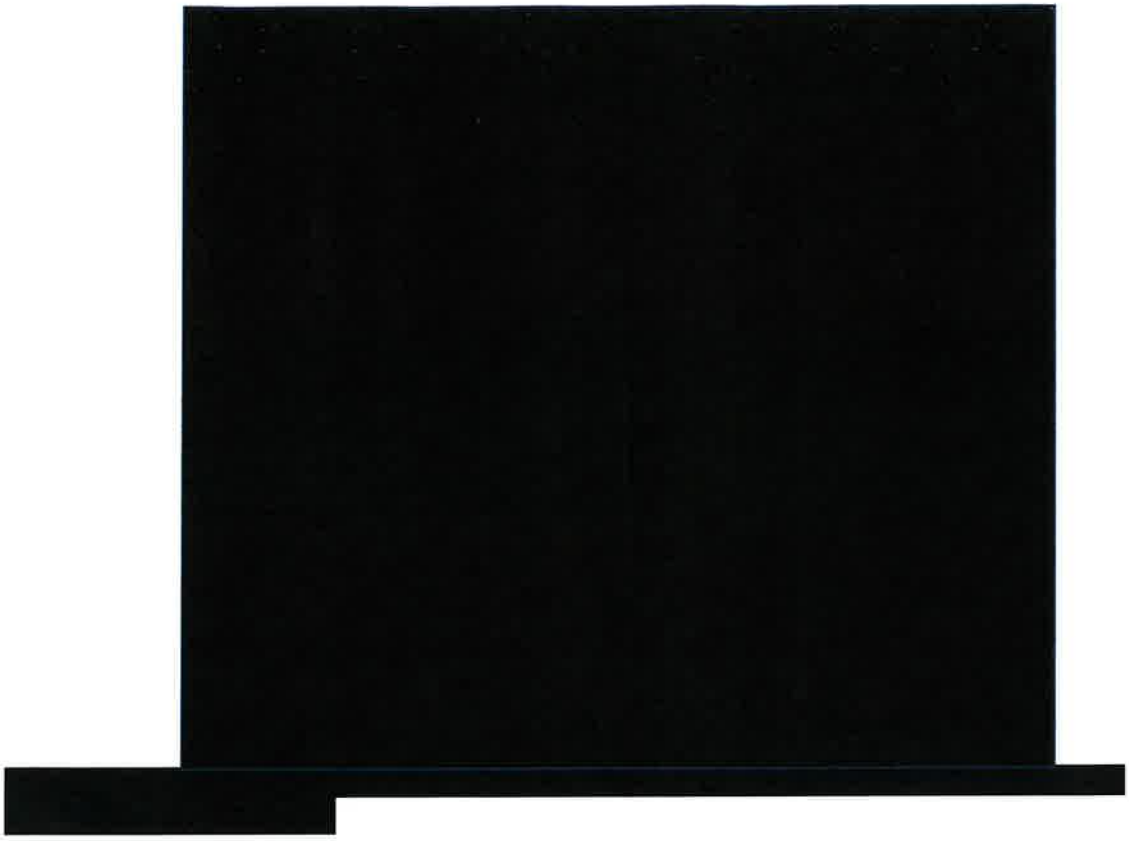
5.2.2 Leads will be placed [redacted]

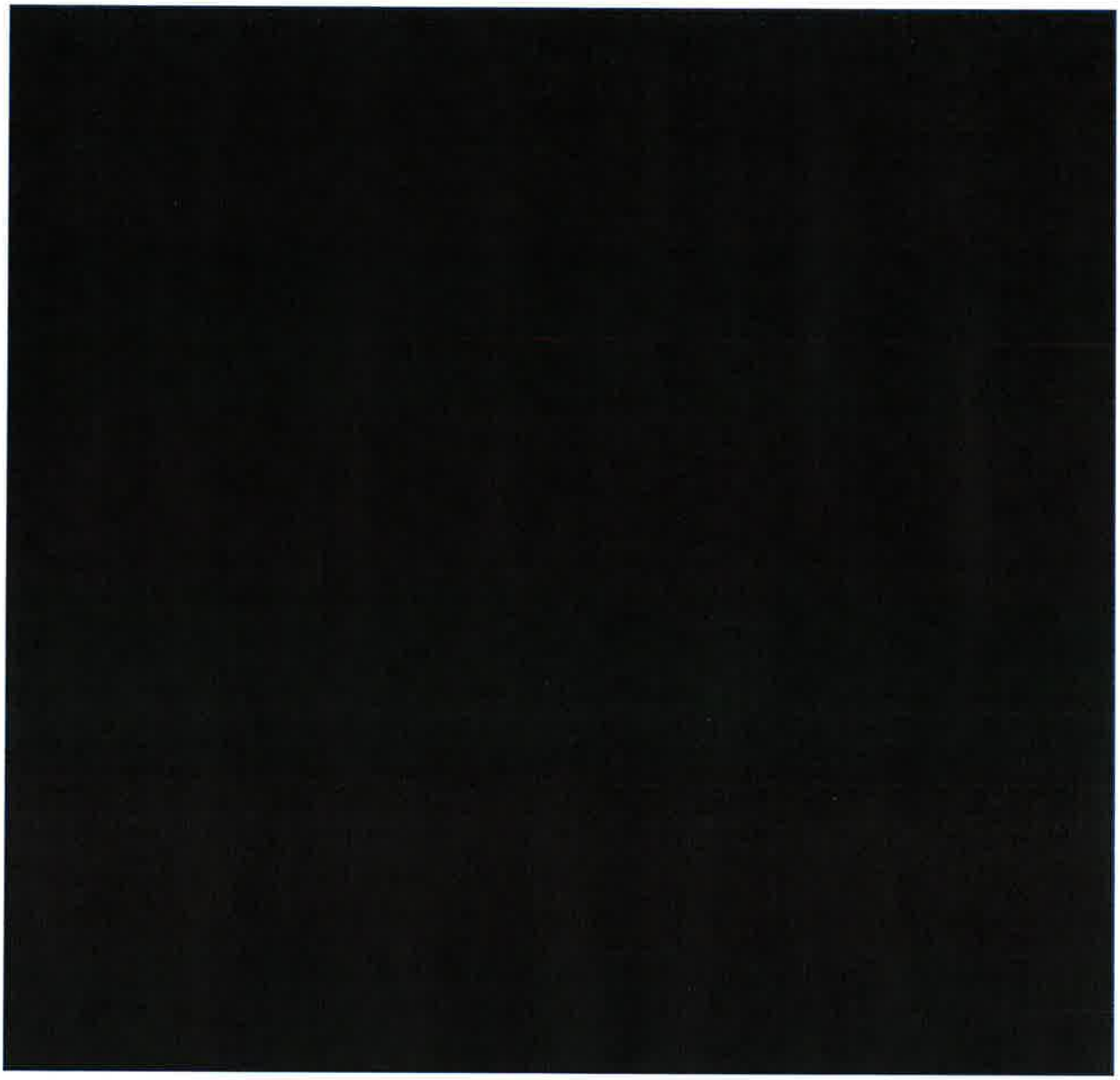
After randomization assignment, subjects will be prepared for the lead placement procedure, which is identical for both groups except for use of active stimulation. [redacted]

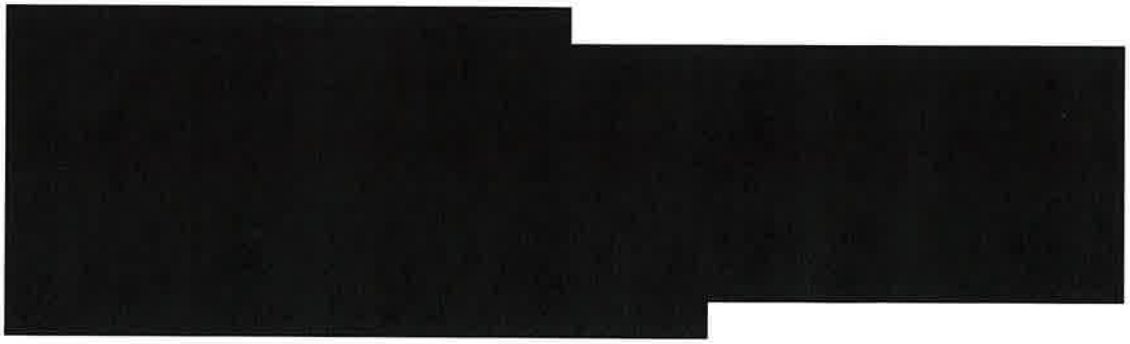
[redacted]

[redacted]









[redacted]

[redacted]

Group #1: Stimulus parameters will be adjusted [redacted]

Group #2: The procedure will be identical to Group #1 except that no active stimulation will be delivered. [redacted]

5.2.6 Treatment period or Subject Disposition

At the end of Visit 2 (and Visit C1 for Group #2 cross-over subjects), there are three options:

1. Proceed to treatment period: [redacted]

2. Return for another Lead Placement visit (V2 or C1):
   If there is not sufficient time [redacted] the investigator may present the subject with the option to return for a repeat lead placement visit.

   [redacted]

3. Discharge from the study: [redacted]

[redacted]

[redacted]

5.2.8 Treatment period

Subjects will be prepared to proceed to the treatment period. [redacted]

[redacted]

[redacted]

[redacted]

5.2.9 Telephone Follow-up

All subjects will receive a Telephone Follow-up 24 - 48 hours after lead placement to query for any adverse device effects (ADE). All ADEs will be followed until resolution. [redacted]

[redacted]

5.3 Visit 3 – 1 Week Post Lead Placement

Subjects will return approximately 1 week after the start of treatment.

[redacted]

5.4 Visit 4 – 2 Weeks Post Lead Placement

The subject will return approximately 2 weeks after the start of treatment.

[redacted]

5.5 Visit 5 – 3 Weeks Post Lead Placement Phone Call

The subject will receive a Telephone Follow Up from the unblinded evaluator approximately 3 weeks after the start of treatment[redacted]

[redacted]

5.6 Visit 6 – 4 Weeks Post Lead Placement

The subject will return approximately 4 weeks after the start of treatment lead placement [redacted]

5.7 Visit 7 – 5 Weeks Post Lead Placement Phone Call

The subject will receive a Telephone Follow Up from the unblinded evaluator approximately 5 weeks after the start of treatment [redacted]

5.8 Visit 8 – 6 Weeks Post Lead Placement

The subject will return approximately 6 weeks after the start of treatment lead placement. [redacted]

5.9 Visit 9 – 7 Weeks Post Lead Placement Phone Call

The subject will receive a Telephone Follow Up from the unblinded evaluator approximately 7 weeks after the start of treatment [redacted]

5.10 Visit 10 – 8 Weeks Post Lead Placement: lead removal and end of treatment (EOT)

The subject will return approximately 8 weeks after the initial lead placement. [redacted] the leads will be removed for both groups, marking

the end of treatment (EOT).

[redacted]

5.11 Visit 11 – Follow-up visit 3 months after start of treatment (SOT)

[redacted]

Following the completion of all outcome measures at Visit 11, subjects will be informed of their group assignment. [redacted]

Group #1 subjects will continue with follow-up Visits 12-14. Group #2 subjects will be given the option to discharge from the study, or crossover to receive active stimulation for an 8-week treatment period. [redacted]. Group #2 subjects that choose to cross over to receive stimulation will continue with Visits C1-C4, then follow-up Visits C5-C8. [redacted]

5.12 Follow-up Phone Call Visits for Group #1: Visit 12 (6-mo after SOT), Visit 13 (9-mo after SOT), Visit 14 (12-mo after SOT)

Group #1 subjects will receive telephone follow-ups at approximately 6 months, 9 months, and 12 months after the start of treatment. [redacted]

[redacted]

5.13 Visit C1: Crossover Lead Placement, Group #2

Visit C1 is similar to the lead placement at Visit 2. [redacted]

Leads will be placed [redacted]

The stimulation parameters will be set [redacted]

For Group #2 subjects who received leads at this visit, the options for subject disposition will be the same as at Visit 2 [redacted]

Subjects will receive a Telephone Follow-up 24 - 48 hours after each Visit C1 (Lead Placement for Group 2 subjects that crossover) to query for any adverse device effects (ADE). All ADEs will be followed until resolution.

5.14 Visit C2 – 2 Weeks Post Lead Placement, Group #2

Subjects will return approximately 2 weeks after the start of crossover treatment (SOCT). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.15 Visit C3 – 4 Weeks Post Lead Placement, Group #2

The subject will return approximately 4 weeks after the start of crossover treatment. [redacted]

5.16 Visit C4 – 8 Weeks Post Lead Placement, Group #2

The subject will return approximately 8 weeks after the start of crossover treatment.

[redacted]

5.17 Follow-up Phone Call visits for Group #2:

Visit C5 (3 months after start of crossover treatment [SOCT]),
Visit C6 (6 months after SOCT),
Visit C7 (9 months after SOCT),
Visit C8 (12 months after SOCT)

Group #2 subjects that crossed over and completed a treatment period with the therapy (Visits C1-C4) subject will receive a Telephone Follow Up approximately 3, 6, 9, and 12 months after the start of crossover treatment [redacted]

[redacted]

[redacted]

[redacted]

5.19 Study Visit Windows

The acceptable windows for each visit are listed in Table 4. The study visit windows in Table 4 are guidelines, but every effort should be made to collect all study data, even if out of window.[redacted]

Table 4 Study Visit Windows

Visit Number	Visit Name	Window
n/a	Consent	[redacted]
1	Baseline	
2	Lead Placement (SOT)	
2.1	Follow-up call	
3	1 week Stimulation	
4	2 week Stimulation	
5	3 week Stimulation call	
6	4 week Stimulation	

7	5 week Stimulation call	[redacted]
8	6 week Stimulation	
9	7 week Stimulation call	
10	8 week Stimulation	
11	3 month follow-up	
Group #1 Follow Up:		
12	6 months follow-up call	[redacted]
13	9 months follow-up call	
14	12 month follow-up call	
Group #2 Crossover/Follow Up:		
C1	Crossover lead placement (SOCT)	[redacted]
C1.1	Follow-up call	[redacted]
C2	2 week Stimulation	
C3	4 week Stimulation	
C4	8 week Stimulation	
C5	3 month follow-up call	
C6	6 month follow-up call	
C7	9 month follow-up call	
C8	12 month follow-up call	

[redacted]

[redacted]

5.21 Subject Compensation

Individuals [redacted] will receive compensation for full participation in all study visits to cover expenses while taking part in this study. [redacted]

[redacted]

All Group #1 and Group #2 subjects will receive:

- [redacted] after the completion of Visit 1
- [redacted] after the completion of Visit 2 Screening
- [redacted] after the completion of Visit 2 Testing
- [redacted] after the completion of each Visit 3, 4, 6, 8, 10, and 11
- [redacted] after the completion of each Visit 5, 7, and 9 phone calls

Group #1 subjects will also receive:

- [redacted] after the completion of each Visit 12-14

Group #2 subjects that crossover to receive stimulation will also receive:

- [redacted] after the completion of Visit C1 Testing
- [redacted] after the completion of each Visit C2-C4
- [redacted] after the completion of each Visit C5-C8 phone calls

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

If a subject participates in an Unscheduled Visit (other than an additional Visit 2), they will receive [redacted] compensation for completion of that unscheduled visit.

[redacted]

6.0 Informed Consent Process

In accordance with applicable regulations, it is the responsibility of the Principal Investigator to give each participant 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. [redacted]

[redacted]

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. The EDC system will be validated prior to being available for data entry at the sites and will include appropriate electronic security measures such as controlled password protected access, storage and back-up on the data on a secure HTTP (SSL) server, and appropriate data entry logic and validation checks.

Paper source documents, where applicable, will be completed and maintained in a fashion that is consistent with accepted Good Clinical Practices. If necessary, corrections to the source documentation will be made by using a single line strikeout with the initials and date of the person making the correction. The corrections will be made so as not to obscure the original data. Correction fluid or correction tape may not be used. Where specified, the Principal Investigator must sign and date the source documentation and questionnaires.

All paper study documentation will be stored in a locked storage facility (either a locked office or a locked cabinet). After subject randomization and through Visit 11, surveys will be administered by a study team member who will not know the randomization assignment of each subject and thus will be designated as a Blinded Evaluator.

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. [redacted]

7.3 Data processing

SPR Therapeutics, Inc. (or their authorized representatives) will be responsible for database creation, generation of database queries, and data analysis. [redacted]

[redacted]

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. [redacted]

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 will be counted as enrolled. [redacted]

7.6 Blinding

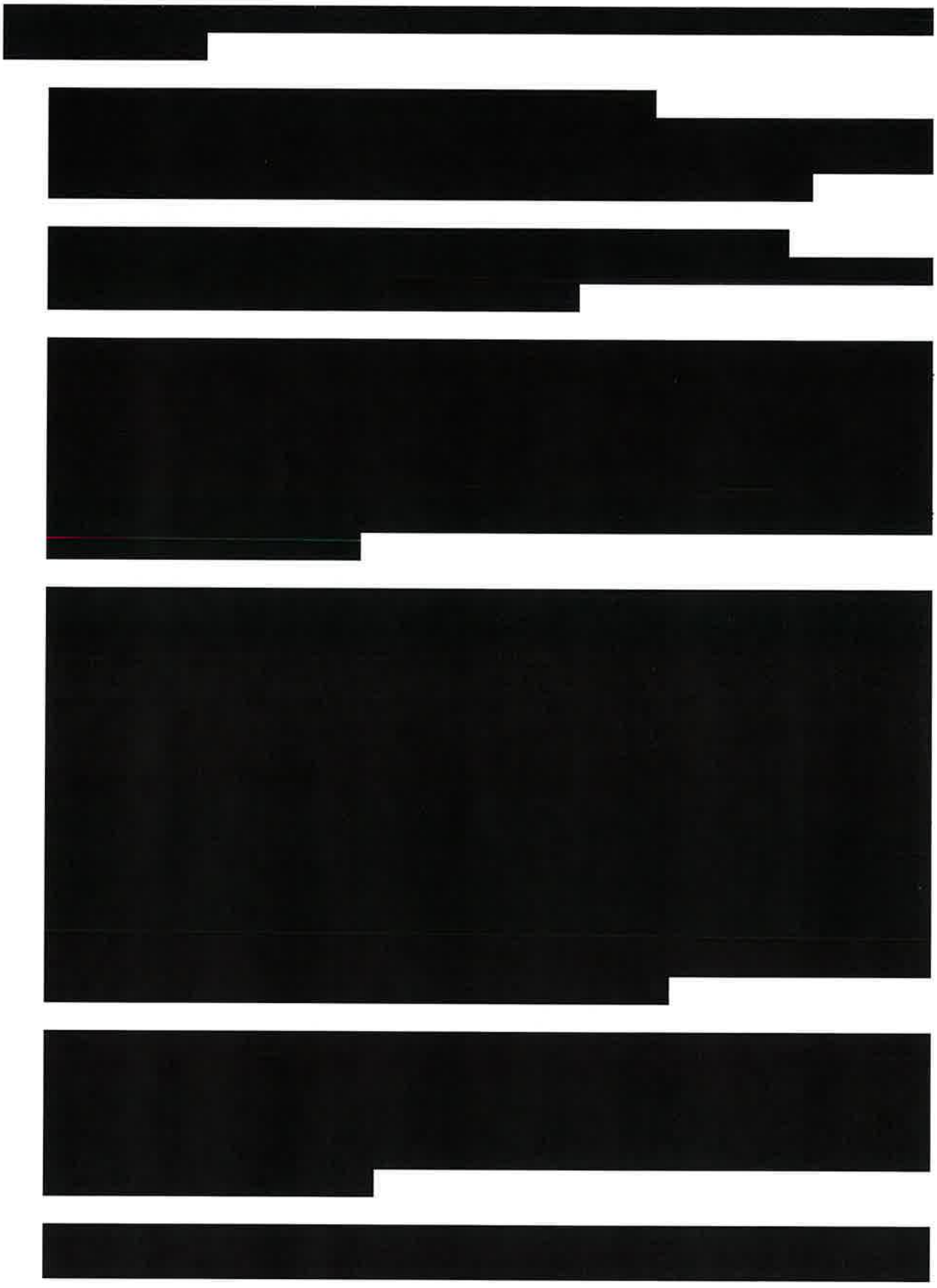
[redacted] Blinding of subjects will not be broken until the subject completes Visit 11 and completes the pain/medication diary, unless necessary for medical reasons and the safety of the subjects

Each site will designate a study team member to serve as the blinded evaluator, who will not know the randomization assignment of the subjects. [redacted]

Unblinded study staff will perform all activities that cannot be performed by the blinded evaluator. [redacted]

8.0 DATA ANALYSIS AND STATISTICAL METHODS

All primary and secondary outcome data will be analyzed and reported. [redacted]



[redacted]

8.3 Safety Endpoint Analysis

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

9.0 Study Training, Monitoring, and Device Accountability

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 the clinical research monitors and the Study Team at each Site.

9.2 Study Monitoring

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 Protocol 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 Electronic Data Capture system.

[redacted]

9.3 Device Accountability

[redacted]

9.4 Designation of 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: 216-378-9116

9.5 Independent Clinical Events Reviewer

An Independent Clinical Events Reviewer (ICER) will be utilized for this study to adjudicate study related adverse events (AEs). AE information, including group assignment, will be provided to the Reviewer. The adjudication by the Clinical Events Reviewer will be the final determination.

10.0 ADVERSE EVENTS AND UNANTICIPATED ADVERSE DEVICE EFFECTS

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 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 that meet the requirements for Medical Device Reporting (MDR) will be entered into SPR's complaint system.

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

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

[redacted]

Table 2: Unanticipated Adverse Device Event Sponsor Contact Information

UNANTICIPATED ADVERSE DEVICE EVENT SPONSOR CONTACT INFORMATION			
Name/Title	**Email address**	**Telephone Number**	**Fax Number**
[redacted]	[redacted]	[redacted]	[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 SPR's standard operating procedures.

11.0 Risk Benefit Analysis

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

11.1 Potential Benefits

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

This research may benefit future patients with postoperative pain following knee replacement surgery.

11.2 Known and Anticipated Risks

The risks listed below are described as common uncommon or rare

[redacted]

[redacted]

[redacted]

[redacted]

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

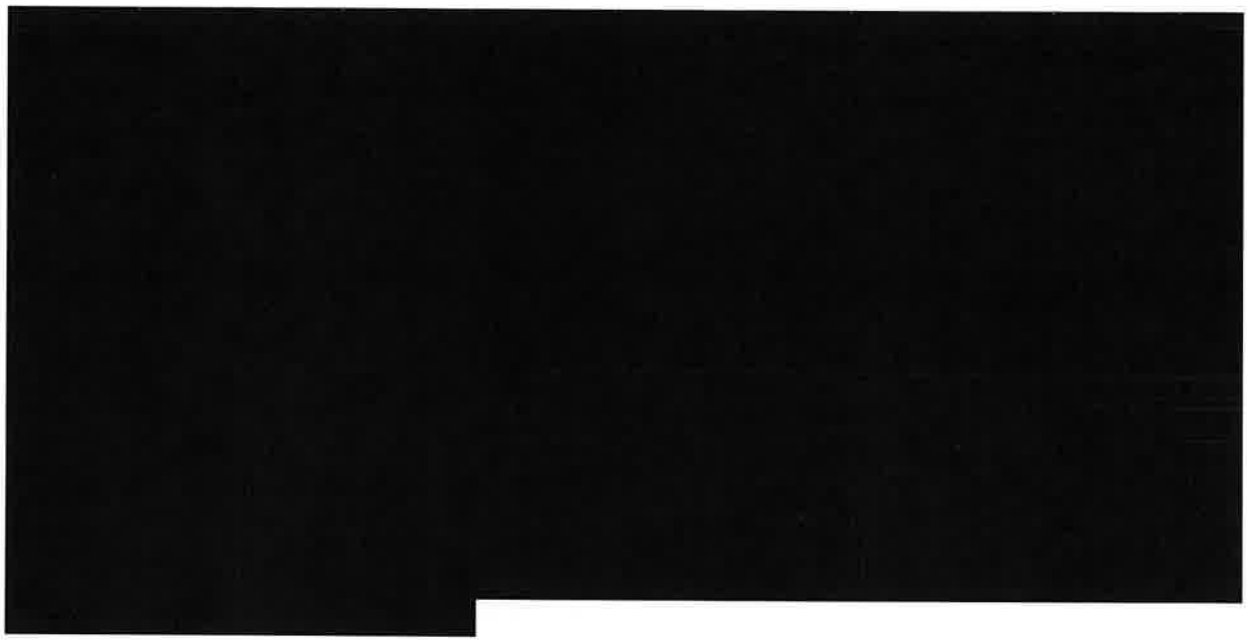
[redacted]

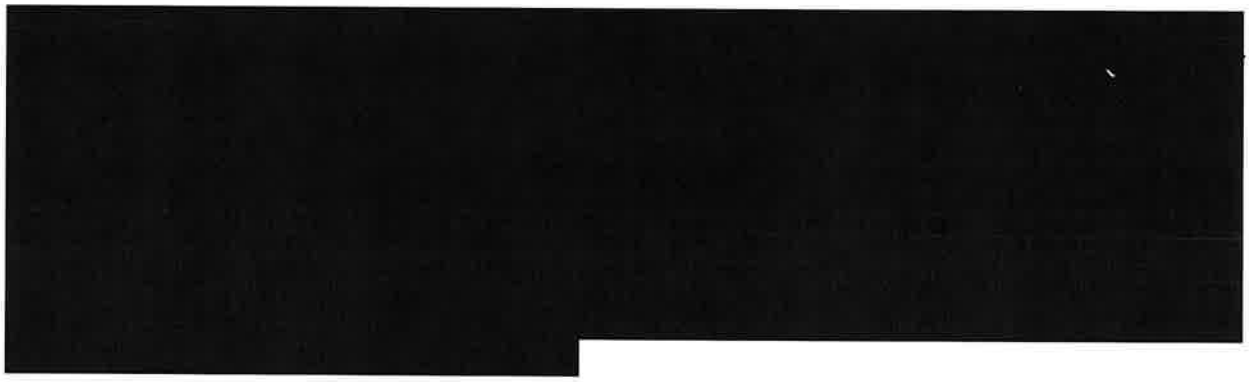
[redacted]

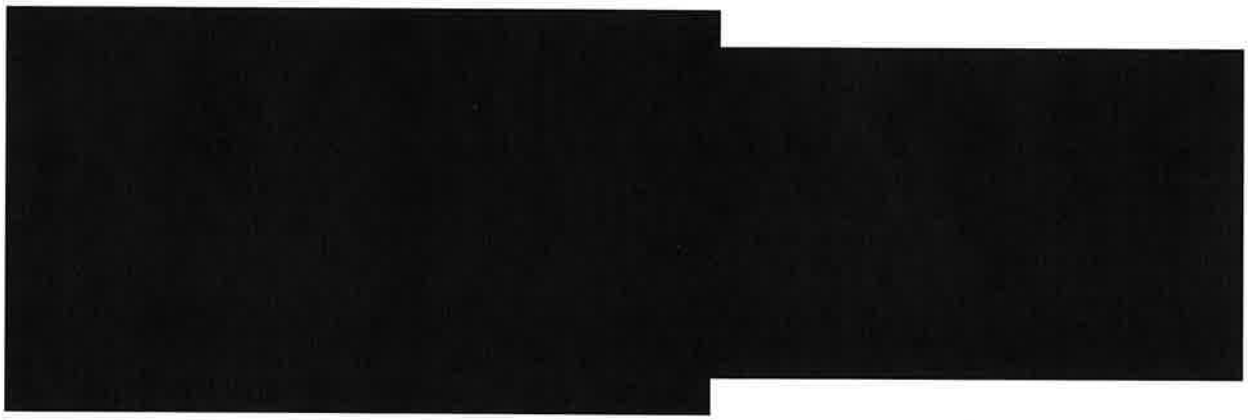
[redacted]

Risk of the percutaneous lead breaking beneath the skin

[redacted]







[redacted]

[redacted]

Risk of skin irritation under the pad, lead connector tape, or bandages

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Risk of discomfort or increased pain

[redacted]

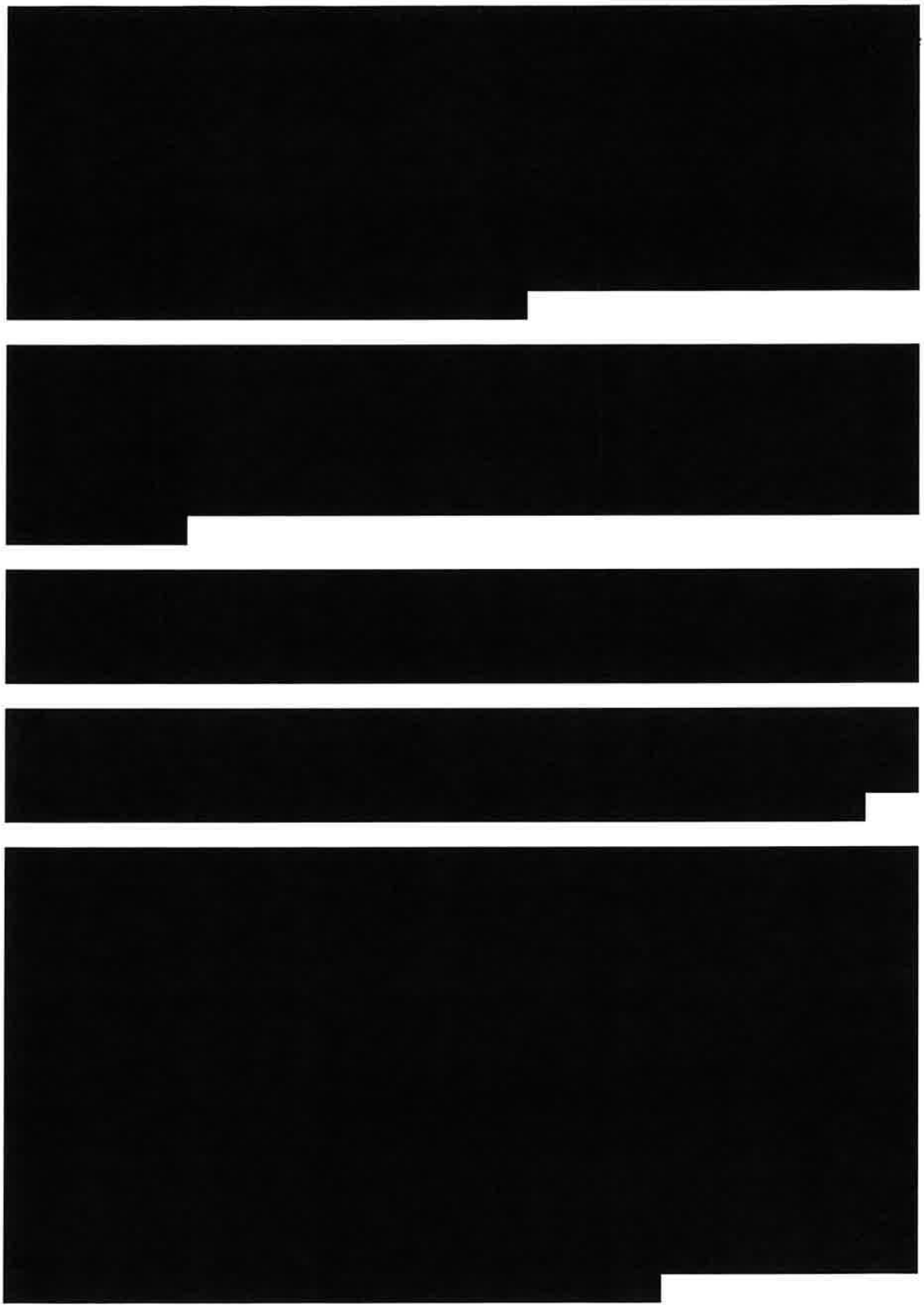
[redacted]

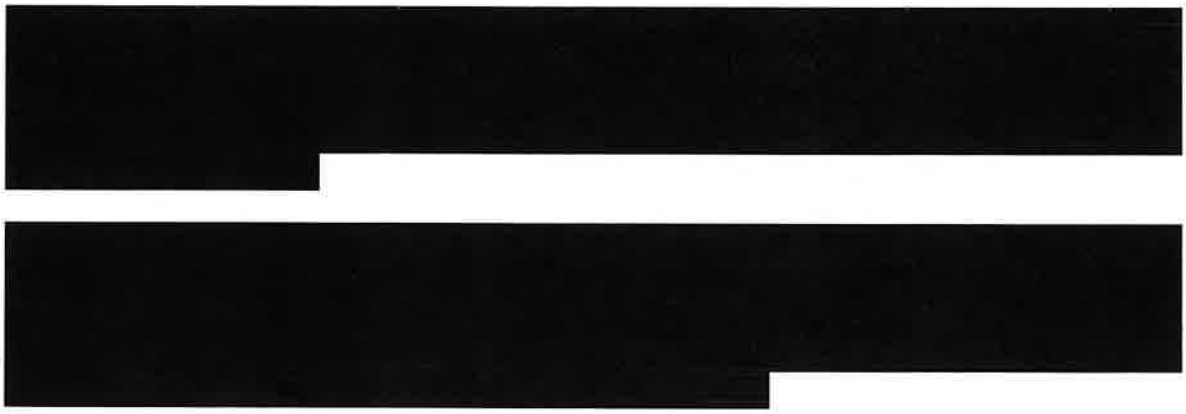
[redacted]

11.3 Risk Analysis

As described above, all efforts will be made to mitigate each potential risk associated with the use of the system. [redacted] The potential risks of participation in this study have been minimized such that they are unlikely to occur and/or have non-serious consequences. [redacted]

11.4 Risk Justification





The potential benefits of this procedure to reduce post-operative pain and opioid use following orthopedic surgery outweigh the risks associated with this procedure and temporary treatment.

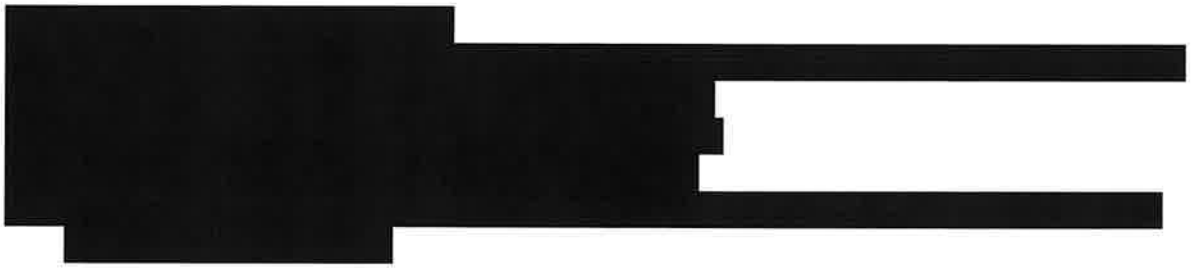
12.0 Study Administration

12.1 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.

12.2 Criteria for Terminating a Subject

SPR Therapeutics reserves the right to terminate a study subject 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.



12.3 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. [redacted]

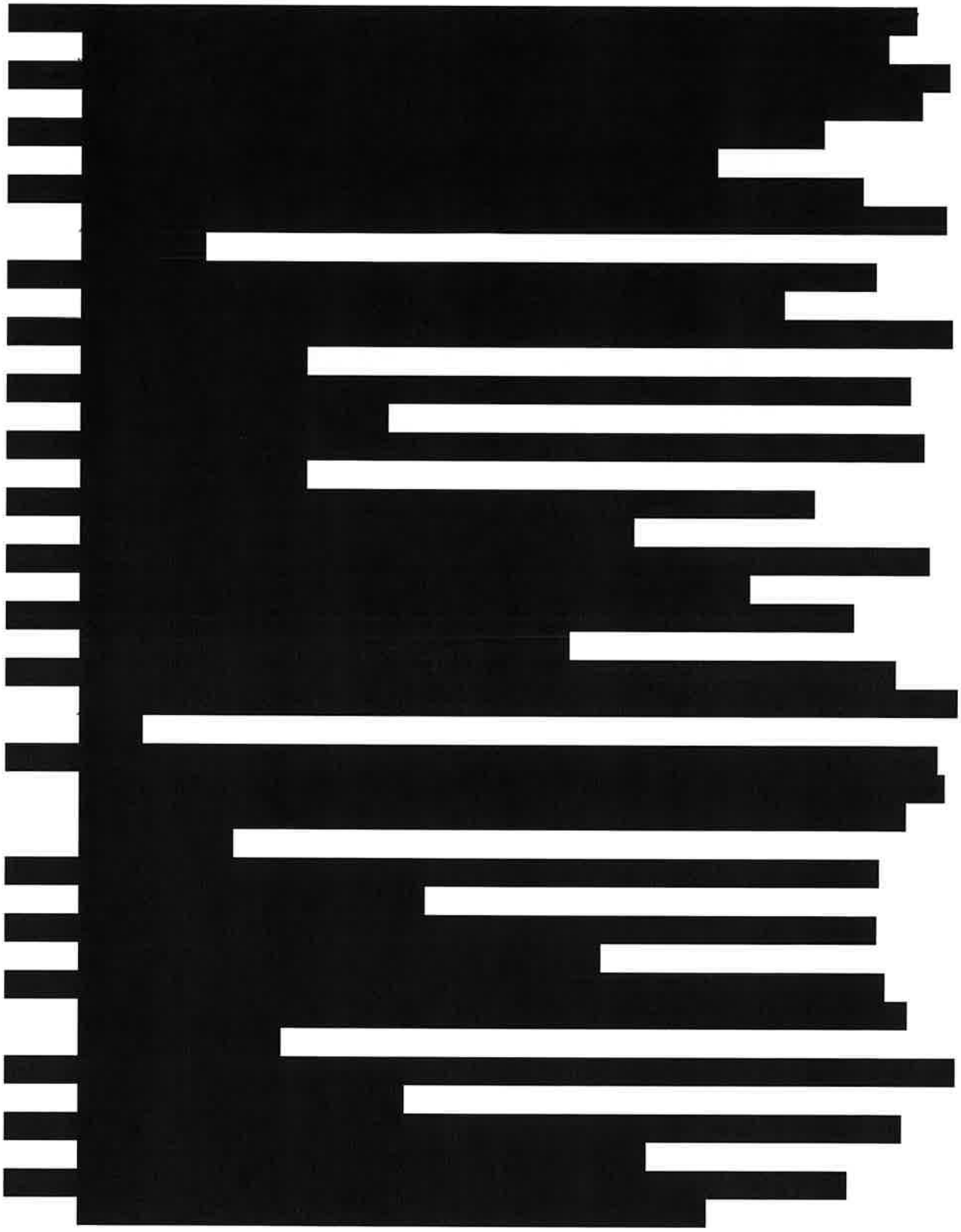
12.4 Criteria for Terminating a Center

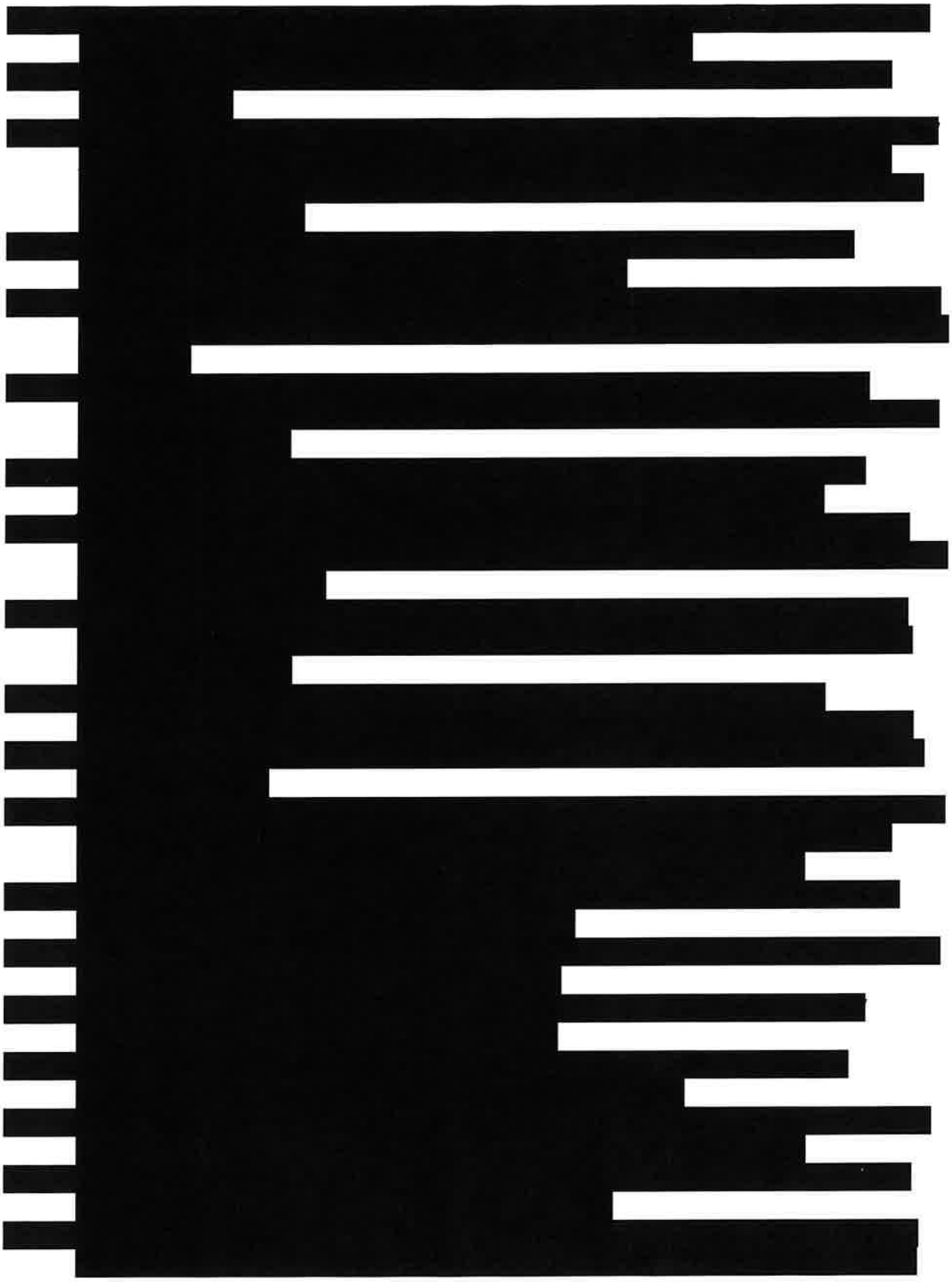
The Sponsor reserves the right to suspend or stop the enrollment of subjects at a study center at any time after the study initiation if no subjects have been enrolled or if enrollment numbers are well below anticipated enrollment expectations. [redacted]

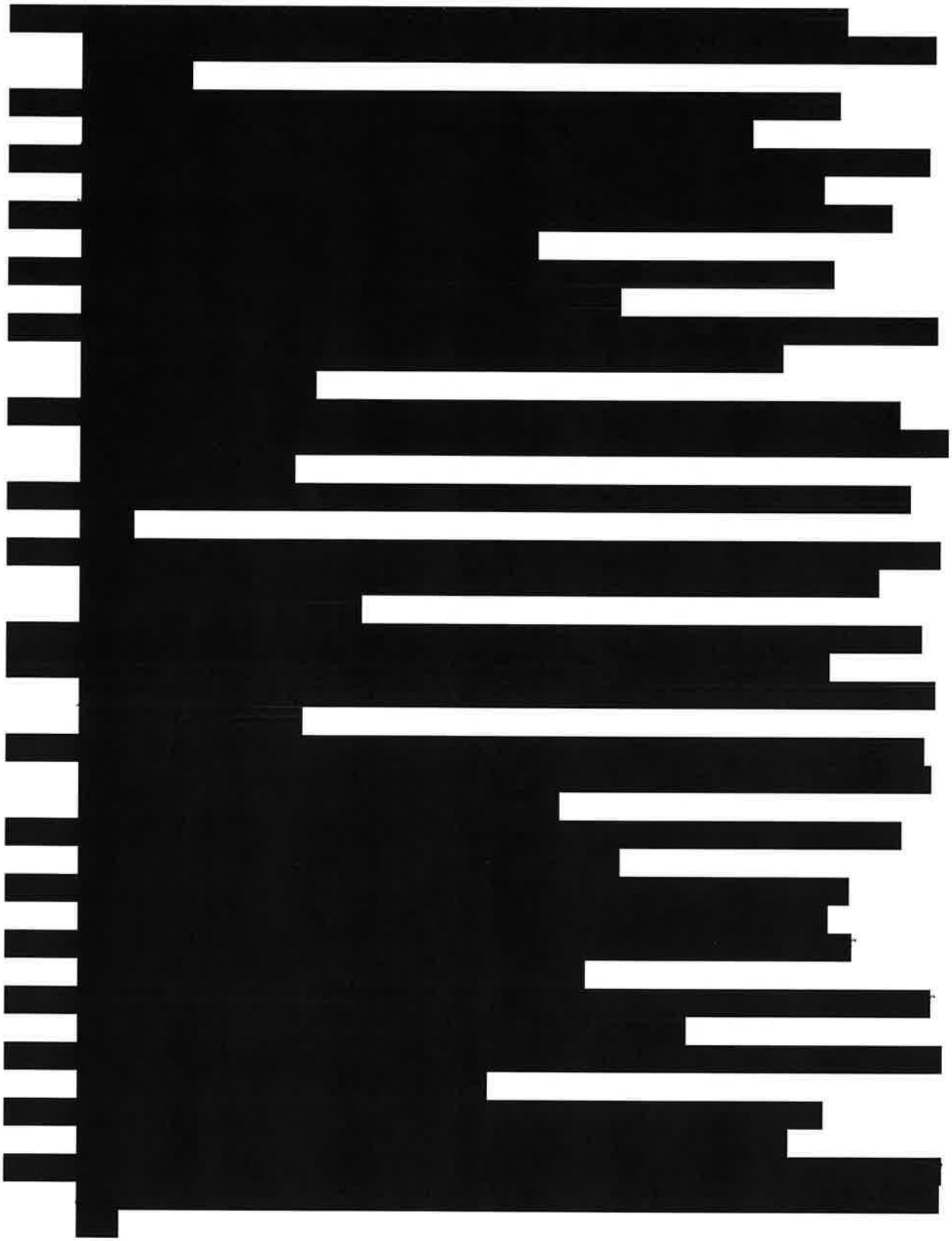
12.5 Investigator Qualifications, Responsibilities, and Training

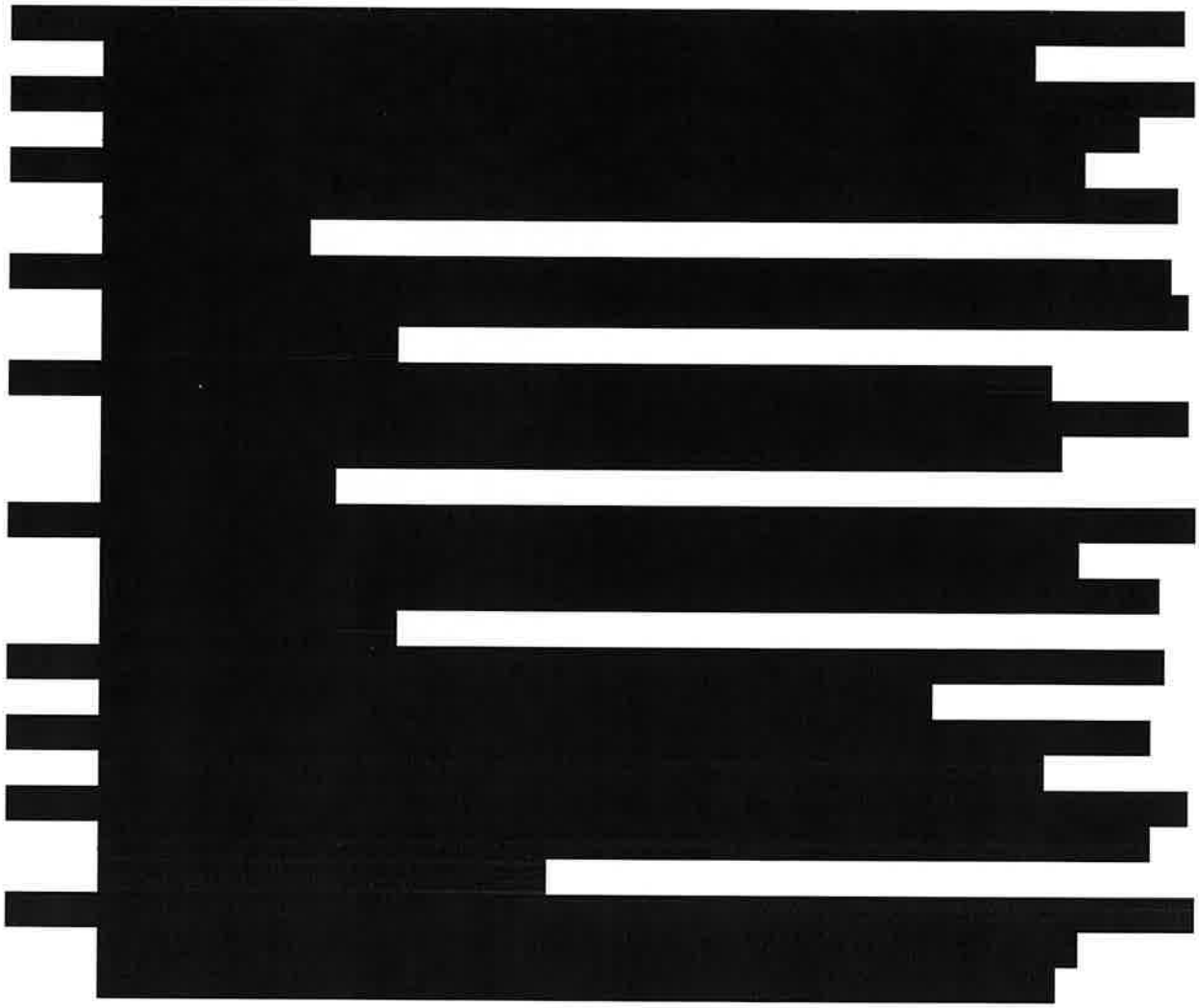
To participate in this study, the Investigator must sign the Investigator Agreement which documents his responsibilities in the study. The Investigator will require training on this study plan and the device. [redacted]

13.0 Bibliography









[redacted]

[redacted]