Official Title:
A Prospective, Comparative Effectiveness Randomized Controlled Trial of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement

NCT#: 03286543

Date: 22 February 2019

A Prospective, Comparative Effectiveness Randomized Controlled Trial of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement

Sponsor:

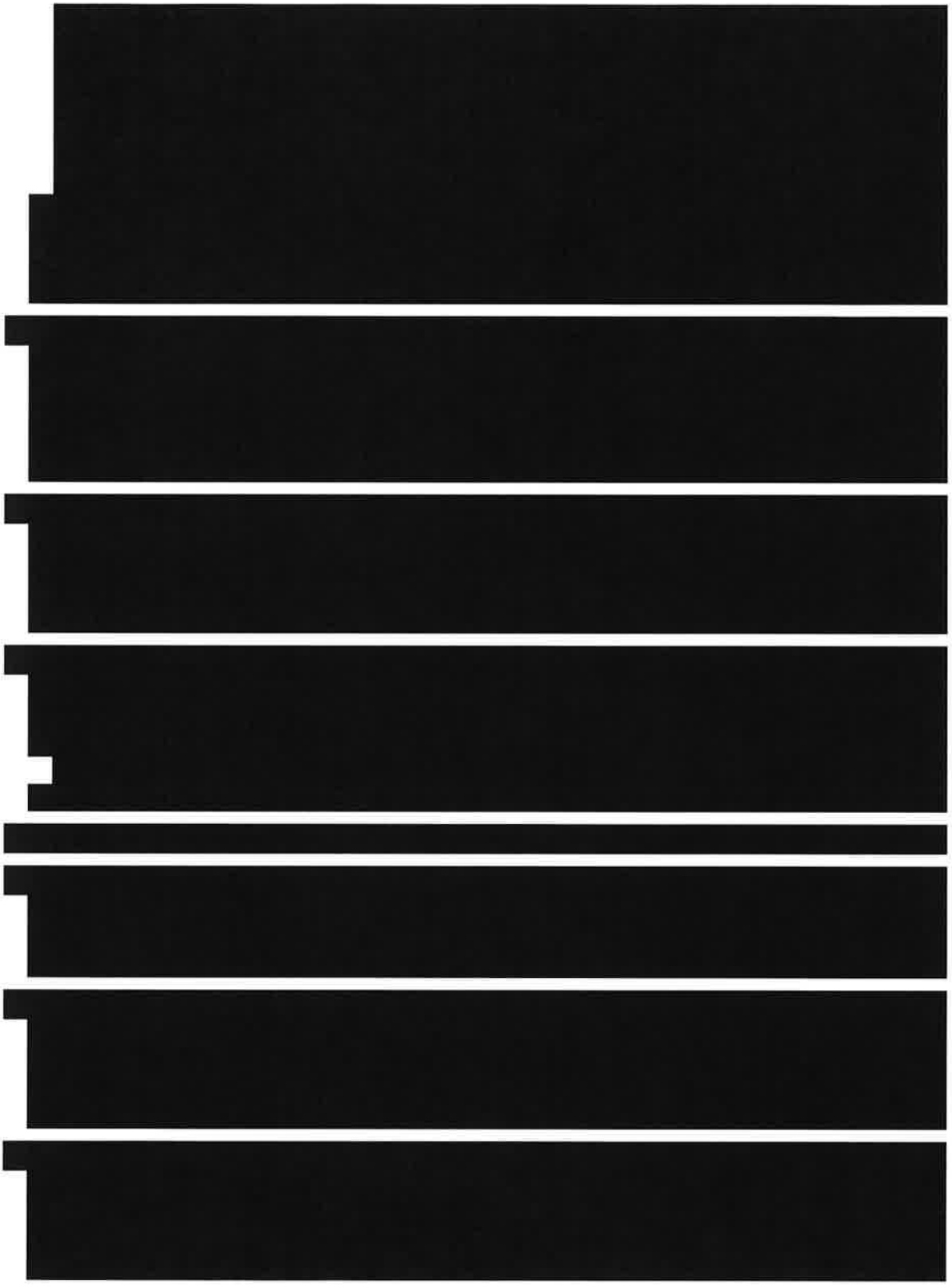
SPR Therapeutics, Inc.
22901 Millcreek Boulevard
Cleveland, OH 44122
Phone: 216-378-9108
Fax: 216-378-9116

Protocol [redacted]

Date

November 18, 2016
November 21, 2016
March 20, 2017
March 15, 2018
February 22, 2019

[redacted]



[redacted]

1.0 List of Abbreviations

Abbreviation	Term
AE	Adverse Event
BPI	Brief Pain Inventory
CRF	Case Report Form
EOT	End of Treatment
INR	International Normalized Ratio
ITT	Intent to Treat
NMES	Neuromuscular Electrical Stimulation
OA	Osteoarthritis
PCS	Pain Catastrophizing Scale
PGIC	Patient Global Impression of Change
PNS	Peripheral Nerve Stimulation
POD	Post-Operative Day
PP	Per Protocol
QoL	Quality of Life
RCT	Randomized Controlled Trial
SOC	Standard of Care
TENS	Transcutaneous Electrical Nerve Stimulation
TKA	Total Knee Arthroplasty
TUG Test	Timed Up and Go Test
WOMAC	Western Ontario and McMaster Universities Arthritis Index

2.0 Protocol Synopsis

Title	A Prospective, Comparative Effectiveness Randomized Controlled Trial of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement
Investigational (Test) Device	SPRINT® Beta Peripheral Nerve Stimulation (PNS) System
Study Design	Prospective, Comparative Effectiveness Randomized Controlled Trial
Primary Study Objective	To determine if the addition of PNS therapy to the site's standard of care for treatment of knee pain following TKA is significantly different than that of the site's standard of care alone.
Study Plan	Individuals undergoing a primary unilateral TKA will be considered for enrollment into the study. After obtaining informed consent, potential subjects will be evaluated for general eligibility. Qualifying subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control). All subjects will receive the site's standard of care (SOC) for the treatment of knee pain before, during, and after the TKA. Subjects assigned to Group #1 will also receive Peripheral Nerve Stimulation Therapy for up to approximately 30 days before the procedure, and again starting immediately after the TKA for a total of up to 60 days. Subjects will receive treatment for 4 weeks post-TKA. At the conclusion of the treatment period, the leads will be removed. Subjects in both groups will receive the site's SOC for treatment of knee pain before, during and after TKA. Subjects will complete a daily diary recording their medication usage and daily Pain. Other outcomes that will be assessed include tests of function, stimulation characteristics, surveys/questionnaires, pain scores and pain treatments. Outcomes will be assessed based on the schedule of study procedures (Appendix A).

Sites (N)	Up to 10 investigational sites
Subjects (N)	Approximately 50 subjects will be enrolled. Subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control).
Inclusion Criteria	• Between the age of 21 and 90 years old • Scheduled to undergo a primary unilateral total knee replacement procedure • 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	• Body Mass Index (BMI) > 40 kg/m^2 • Conditions that place the subject at increased risk of infection in the opinion of the investigator, [redacted] • History of valvular heart disease • Implanted cardiac pacemaker/defibrillator or Deep Brain Stimulator • Bleeding disorder **OR** INR ≥ 1.5 for those on warfarin (Group #1, only) • Confounding conditions [redacted] or central nervous system disorders • History of nerve damage [redacted] • Allergy to skin surface electrodes and/or medical-grade adhesive tapes • Contraindications to the proposed anesthetic protocol during lead placement [redacted] • Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator • Prisoners, minors or individuals that report to investigators (e.g., students, employees) • Pregnant (Group #1, only) • History of substance abuse within 6 months • Potential secondary gain issues (*e.g.*, pending claims or receiving disability)
Primary Safety Endpoint	Occurrence of device-related adverse events.
Primary Clinical Endpoint	The primary clinical endpoint is average daily pain while walking. Subjects will record [redacted] pain while walking [redacted] in a daily diary [redacted] The difference in the [redacted] pain scores between the two groups (Treatment vs. Control) will be calculated to determine if PNS Therapy provides a [redacted] reduction in [redacted] daily pain while walking.
Secondary Endpoints	Pain-related outcomes

	• Pain intensity over the last 24 hours as recorded as **Average pain** [redacted] • Pain intensity [redacted] • **Pain right now** [redacted] • **Cumulative analgesic usage** • **Opioid-related side effects** [redacted] Functional outcomes • **Timed Up and Go** [redacted] • **6 minute walk test** [redacted] • Change in pain, physical function, and stiffness [redacted] • **Patient Global Impression of Change (PGIC)** • **Pain Catastrophizing Scale (PCS)** • **Time to meet recovery milestones** [redacted] • [redacted] **Subject Satisfaction Survey** • **Inpatient Pain Management Experience Survey** • **Compliance** [redacted] • [redacted] **Physical Therapy Sessions**
Exploratory Measurements	• [redacted] primary and secondary endpoints at study intervals not specified • Pain coverage • [redacted] sensation coverage of leg [redacted] • Clinician Satisfaction Survey
Key Demographic Information	• Body Mass Index (BMI) • Surgical approach [redacted] • Use of post-operative drains • [redacted] knee implant used [redacted]

3.0 General Information

3.1 Title of Investigation

A Prospective, Comparative Effectiveness Randomized Controlled Trial of SPR peripheral nerve stimulation (PNS) therapy for the treatment of pain following total knee arthroplasty (TKA) utilizing preoperative lead placement

3.2 Sponsor Name and Address

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

3.3 Study Materials

The SPRINT® Beta Peripheral Nerve Stimulation (PNS) System: [redacted]

3.4 Study Objective

To compare the effectiveness and safety of PNS therapy in conjunction with the SOC to SOC alone for the treatment of knee pain following TKA.

4.0 Introduction and background

4.1 Introduction

The goal of this research is to gather data regarding the safety and effectiveness of PNS therapy for the treatment of pain following total knee arthroplasty (TKA; a.k.a. total knee replacement).

[redacted]

[redacted]

[redacted]

The hypothesis is that percutaneous stimulation will [redacted] produce greater pain relief than with standard of care alone.

4.2 Background

Postoperative pain following total knee arthroplasty is a substantial medical problem

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

The proposed method aims to relieve postoperative pain following TKA by delivering electrical stimulation through percutaneous [redacted] SPRINT MicroLeads [redacted]

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

The proposed method may provide immediate pain relief [redacted]

[redacted]

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

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

Electrical stimulation was delivered through [redacted] leads

[redacted]

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

[redacted]

[redacted]

Summary

[redacted]

The proposed study will determine if this therapy in combination with the site's respective SOC can produce significant reductions in postoperative pain following TKA as compared to the site's SOC alone.

5.0 Study Outcomes and Exploratory Measures

5.1 Overview

In both groups, outcomes and exploratory measures will be collected before and after TKA surgery (see Appendix A for schedule of study procedures) and include

1. Average Pain while walking, at rest, and average over the last 24 hours [redacted]
2. Pain right now [redacted]
3. Cumulative analgesic usage
4. Opioid-related side effects [redacted]
5. Timed Up and Go [redacted]
6. Six Minute Walk Test
7. [redacted]
8. Patient Global Impression of Change (PGIC)
9. Pain Catastrophizing Scale (PCS)
10. Time to meet recovery milestones
11. Subject satisfaction survey
12. Inpatient Pain Management Experience Survey
13. Pain Distribution
14. [redacted] sensation [redacted]
15. Clinician satisfaction survey
16. Compliance [redacted]
17. [redacted] Physical Therapy Sessions

5.2 Primary Outcome

The primary outcome of this study will be the average daily pain while walking over the first 4 weeks following TKA surgery. [redacted]

5.3 Secondary Outcomes

Secondary outcome measures will provide additional information on pain and function.

[redacted]

The [redacted] is a widely used assessment designed to measure pain intensity and the interference of pain on daily activities and moods [redacted]

Cumulative Analgesic usage

The amount and type of analgesic used by the subject will be recorded daily in a diary before TKA surgery, from the subject's records during their hospital stay, in daily diaries after discharge from the hospital, and at each visit following End of Treatment. [redacted]

Opioid-related Side Effects

Opioid pain medications are associated with a wide variety of side effects. Common side effects include nausea and vomiting, constipation, urinary retention, pruritus, drowsiness, and respiratory depression. [redacted]

Timed Up and Go

The is an objective measure of mobility.

Six minute walk test

The records the total distance the subject can walk in 6 minutes.

The is a widely-used validated questionnaire to evaluate patients with osteoarthritis of the knee and consists of 24 items evaluating pain (5 items), stiffness (2 items), and physical functional disability (17 items)

Patient Global Impression of Change (PGIC)

Participant ratings of global improvement are one of the core outcome domains in chronic pain studies (Dworkin *et al.* 2005).

Pain Catastrophizing Scale (PCS)

The PCS is a widely-used, validated and reliable 13-question instrument to assess rumination (4 questions), magnification (3 questions), and helplessness (6 questions) (Sullivan, 2009.; Osman *et al.* 1997).

Time to Meet Recovery Milestones
The time until the subject meets criteria related to hospital discharge will be measured. [redacted]

Subject Satisfaction Survey
A survey will be administered to assess subject satisfaction with the study and postsurgical pain therapies.

Inpatient Pain Management Experience Survey
This survey is comprised of a subset of questions from the Hospital Consumer Assessment of Healthcare Providers and Systems. This survey will be administered to assess subject satisfaction with pain management during their time in the hospital for TKA surgery.

Compliance
[redacted] SPRINT Beta stimulator [redacted] subject compliance [redacted]

[redacted] *Physical Therapy Sessions* [redacted] physical therapy sessions [redacted]

5.4 Exploratory Measures

[redacted] *primary and secondary endpoints at other study intervals*
The primary and secondary endpoints [redacted] at other study intervals not listed above.

Pain Distribution
Subjects will be asked where they are experiencing pain in the lower limbs.

[redacted] *sensation coverage* [redacted] comfortable sensations.

Clinician satisfaction survey
A sponsor-developed Clinician Satisfaction Survey will be administered. [redacted]

[redacted]

5.5 Safety Endpoint

The primary safety endpoint is the occurrence of protocol-related adverse events. [redacted]

6.0 Device Description

6.1 Overview

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.0 Study Scope

7.1 Number of Sites

Up to 10 investigational sites.

7.2 Number of Subjects

Up to 50 subjects will be enrolled in this study. All subjects will receive the site's SOC for the treatment of knee pain before, during and following TKA. Subjects assigned to Group #1 will also receive PNS Therapy before and after TKA. All subjects who sign an informed consent form will receive a subject ID number. Qualifying subjects will be randomized to either Group #1 (Treatment) or Group #2 (Control). [redacted]

[redacted]

8.0 Study Protocol

8.1 Overview

This study is a prospective randomized controlled trial to determine if the treatment effect of PNS therapy plus each site's standard of care (SOC) for treatment of knee pain following total knee arthroplasty (TKA) is significantly different than that of the site's SOC alone.

8.2 Study Population

Prospective subjects will be screened for eligibility into the study from the available pool of candidates who are scheduled to undergo a primary unilateral TKA. Subjects will be screened using the Eligibility criteria listed in section 8.3. Recruitment materials will be provided to aid in subject enrollment. All recruitment materials will be IRB approved prior to their use.

8.3 Eligibility

8.3.1 Inclusion Criteria

1. Between the age of 21 and 90 years old
2. Scheduled to undergo a primary unilateral total knee replacement procedure
3. Able to understand and provide written consent
4. Able to comply with all study requirements (e.g., if needed, has a caregiver to assist)

8.3.2 Exclusion Criteria

1. Body Mass Index (BMI) > 40 kg/m^2
2. Conditions that place the subject at increased risk of infection in the opinion of the investigator, [redacted]
3. History of valvular heart disease
4. Implanted cardiac pacemaker/defibrillator or Deep Brain Stimulator
5. Bleeding disorder **OR** INR ≥ 1.5 for those on warfarin (Group #1, only)
6. Confounding conditions [redacted] or central nervous system disorders
7. History of nerve damage [redacted]
8. Allergy to skin surface electrodes and/or medical-grade adhesive tapes
9. Contraindications to the proposed anesthetic protocol [redacted]
10. Any other medical condition that may interfere with ability to participate in a clinical trial as determined by the Investigator
11. Prisoners, minors, or individuals that report to investigators (e.g., students, employees)
12. Pregnant (Group #1, only)
13. History of substance abuse within 6 months
14. Potential secondary gain issues (*e.g.*, pending claims or receiving disability)

8.4 Concurrent Medications and Non-Drug Therapies

Subjects in both groups will receive the site's SOC, which may include medication and/or non-drug therapies. However, subjects in both groups should not perform any rehabilitation activities that may conflict with the device Instructions for Use [redacted] during the study before and up to 4 weeks after the TKA. In addition, subjects in both groups will not be

allowed to use other electrical stimulation therapies [redacted] before and up to 4 weeks after their TKA. All interventions targeting pain control will be recorded on the appropriate pages of the CRF.

8.5 Study Plan

The study includes 11 Visits. Appendix A provides schedules of the study procedures for both groups.

[redacted]

8.5.1 Visit 1: Consent and Randomization

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

[redacted] Subjects will receive a one-week daily diary to be completed prior to Visit 2.

8.5.2 Visit 2: Lead Placement Visit (Group #1 only) and Check-in Call (Both Groups)

[redacted]

[redacted]

[redacted] At the conclusion of the Lead Placement Visit, subjects in Group #1 will either:

a. Proceed to treatment phase:
(i) Subjects with acceptable lead placement and stimulation parameters will be prepared to proceed to the treatment phase (See Below). These subjects will start completing a daily diary.

OR

b. Return for another Visit 2:
(i) If there is not sufficient time to complete lead placement or the testing, or if the subject does not respond to stimulation, the investigator may present the subject with the option to return for a repeat lead placement visit. [redacted]

OR

c. Terminate from the Study:
(i) If the subject does not wish to continue with further lead placement or if an additional lead placement visit is needed [redacted], they will be terminated from the study if no adverse events (AE) are noted at the 24-48 hour telephone Check-In Call. If an AE is noted, the subject will be followed until the AE resolves.

Treatment Phase:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5.4 Visit 3: Day of TKA

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.5.5 Visit 4: Daily In-Hospital Visits: (Visits 4a, b, c, etc.)

[redacted]

[redacted]

8.5.6 Visits 5-7: Weeks 1-3 Post-TKA

[redacted]

[redacted]

8.5.7 Visit 8: 4 weeks Post-TKA

[redacted]

8.5.8 Visits 9-10: Follow-up Visits

Visits will occur at 2 months (Visit 9) and 3 months (Visit 10) after TKA surgery. [redacted]

8.5.9 Visit 11: 12 months post-TKA Visit

[redacted]

8.5.10 Unscheduled Visits/Lead Replacements

Subjects may require an unscheduled visit if they experience:

- a technical issue with the stimulation system that the clinical staff has difficulty resolving or desire adjustments to stimulation parameters. [redacted]
- desire assistance with a bandage change [redacted]
- require a lead [redacted]
- experience an adverse event which requires further evaluation by the clinical study staff.

[redacted]

8.6 Study Visit Windows

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

Table 1 Study Visit Windows

Visit Number	Visit Name	Window
1	Consent and Randomization Visit	[redacted]
2	Lead Placement Visit[T] and Check-in Call	[redacted]
3	Day of TKA (POD 0) Visit	[redacted]
4a, b, c…	Daily in-hospital Visits	[redacted]
5	1 week post-TKA Call	[redacted]
6	2 weeks post-TKA Visit	[redacted]
7	3 weeks post-TKA Call	[redacted]
8	4 weeks post-TKA Visit (EOT[T])	[redacted]
9	2 months post-TKA Call	[redacted]
10	3 months post-TKA Call	[redacted]
11	12 months post-TKA Call	[redacted]

[T] Treatment Group (Group #1) Only

8.7 Study Duration

The duration of this study is expected to be 2 years. [redacted]

8.8 Early Termination

[redacted]

8.9 Subject Compensation

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

- [redacted] after the completion of Visit 1
- [redacted] after the completion of Visit 2
- [redacted] after the completion of each Visit 3, 4 (only one instance), 6, and 8
- [redacted] after the completion of each Visit 5, 7, 9 10, and 11

If a subject in Group #1 volunteers to participate in an additional Visit 2 (returns for another session of stimulation testing or for a lead replacement), the subject will receive an [redacted] compensation at the completion of that visit. All requirements for Visit 2 will be repeated.

[redacted]

9.0 Data Management

9.1 Subject Screening and Identification Log

A subject screening log will be completed at the investigational site for all subjects who were considered for the study. Those individuals who are excluded will be listed along with the reason for exclusion. [redacted]

The Subject Identification log will be completed for subjects enrolled in the study.

9.2 Data Collection

Case Report Forms (CRFs) will be completed for each subject who signs an informed consent form up until the point of discharge from the study. CRFs will be completed and maintained in a fashion that is consistent with accepted Good Clinical Practices. All paper documents will be completed in permanent blue or black ink and all entries will be made in a legible fashion. If necessary, corrections will be made by using a single line strikeout with the initials and date of the person making the correction. The corrections will be made so as not to obscure the original data. Correction fluid or correction tape may not be used. All paper study documentation will be stored in a locked storage facility (either a locked office or a locked cabinet).

9.3 Subject Numbering

All subjects who sign an informed consent will be given a unique alpha - numerical Subject ID number. [redacted]

[redacted]

9.4 Confidentiality of Data

Every effort will be made to protect subject confidentiality. Subject names and personal identifiers will not appear in any publications resulting from this work. [redacted]

9.5 [redacted]

[redacted]

[redacted]

[redacted]

10.0 Data Analysis

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

10.1 Analysis of Outcomes and Exploratory Measures

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

[redacted] "Average Pain" [redacted] will be measured daily in both groups for 7 days prior to Visit 2, for 7 days prior to the TKA, and for the first 4 weeks post-TKA. [redacted] An overall mean across all subjects for the first 4 weeks following TKA surgery will be calculated [redacted]. The average [redacted] score over the 4 weeks will be compared between Groups. [redacted]

[redacted]

At several visits, subjects will be asked to report their weekly "Average Pain" [redacted] The mean [redacted] will be calculated and compared between the Groups.

Pain treatments and analgesic usage will be recorded. Changes in opioid usage may be calculated using morphine equivalent dosing (MED). [redacted] subjects taking opioids will be queried for side effects associated with opioids. [redacted] These pain treatment and analgesic-related outcomes will be compared between the Groups.

Functional tests performed during the study will include the Timed Up and Go [redacted] and the Six-Minute Walk Test. The data from these tests will be analyzed [redacted]

Surveys performed during the study will include the [redacted] Patient Global Impression of Change (PGIC), time to meet recovery milestones, Inpatient Pain Management Experience Survey, Subject Satisfaction Survey, and Clinician Satisfaction Survey. [redacted]

Subjects will be asked to report the number of Physical Therapy Sessions they attended each week post-TKA. [redacted]

Throughout the study, subjects will answer questions to describe their pain distribution and stimulation-evoked comfortable sensation (Group #1 only) coverage. [redacted]

The number of hours of stimulation delivered (Group #1 only) as measured by the stimulator will be recorded throughout the study. [redacted]

10.2 Plan to maximize subject retention and minimize loss of data

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

[redacted]

10.3 Safety Endpoint Analysis

Adverse events will be documented (as defined in Section 12.0), reported, and categorized so that the safety profile of this approach may be further understood. Knowledge gained from this study will further refine consent forms and the risk benefit profile for future studies.

10.4 Per Protocol and Intent to Treat Analyses

Analyses of the primary and secondary effectiveness endpoints will be conducted on the intent-to-treat (ITT) population and the per-protocol (PP) population at each specified study interval defined as follows:

PP Population: [redacted]

ITT Population: [redacted]

11.0 Study Monitoring

11.1 Training

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

11.2 Routine Monitoring

Monitoring visits to the Investigational Site will be conducted periodically, as determined by the rate of subject enrollment, during the study to ensure that the most currently approved version of the Investigational Plan is being followed and that the site is in adherence with all Good Clinical Practices and any specific study Data Monitoring Plan that is in place. In addition, source documents will be reviewed for accuracy against data found on the CRFs. [redacted]

[redacted]

11.3 Device Accountability

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

11.3.1 Returning used devices to SPR Therapeutics

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

Stimulators and Components

Disposal of all System components must comply with national and local laws governing the disposal of biohazardous waste. [redacted]

[redacted]

[redacted]

11.4 Designation of Study Monitor

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

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

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

12.0 Adverse Events and Unanticipated Adverse Device Effects

Adverse events (AEs) that occur during the study will be captured on CRFs. Specific details regarding any observed AE will be collected on a separate Adverse Event Form. The severity of each Adverse Event will be collected as well as its relationship to the System. AEs will be classified as mild (event that causes mild discomfort or inconvenience and resolves without treatment), moderate (event that requires medical intervention or medication to treat), or severe (event that requires intervention to prevent permanent impairment or damage, an event that requires or prolongs hospitalization, or an event that is disabling, causing permanent damage, life threatening, or causing death). Adverse events will also be classified as serious or non-serious. Any necessary treatment or intervention required and the resolution status of the adverse event will also be documented. Adverse Events will be followed to resolution. Side effects from narcotic therapy will be collected but not reported as adverse events. Common symptoms after TKA surgery related to the normal healing process (i.e., swelling, bruising, stiffness, incision tenderness, drainage, etc.) will also not be reported as adverse events unless they meet the definition and criteria for AE reporting

An Adverse Device Effect (ADE) is a device-related Adverse Event. All ADE's are further categorized as anticipated or unanticipated. Any ADE's specified in the Risk Analysis of this Investigational Plan will be considered "anticipated". All other ADE's are considered "unanticipated". Anticipated events that occur with a greater frequency than expected are also considered unanticipated.

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

[redacted]

Table 2 Unanticipated Adverse Device Event Sponsor Contact Information

UNANTICIPATED ADVERSE DEVICE EVENT SPONSOR CONTACT INFORMATION			
Name/Title	**Email address**	**Telephone Number**	**Fax Number**
[redacted]	[redacted]	[redacted]	[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 device related, will be reported as well. SPR Therapeutics is responsible for furnishing the required information to the appropriate regulatory authorities.

13.0 Risk Benefit Analysis

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

13.1 Potential Benefits

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

If the investigational treatment is successful, subjects in Group #1 may experience some or all of the following benefits during and/or after stimulation:

- A reduction in the degree of pain [redacted].
- [redacted]
- [redacted]

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

13.2 Known and Anticipated Risks

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

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

Risk of the percutaneous lead breaking beneath the skin

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Risk of skin irritation under the SPRINT Beta pad, bandages, or belt

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Risk of discomfort or increased pain

[redacted]

[redacted]

[redacted]

13.3 Risk Analysis

As described above, all efforts will be made to mitigate each potential risk associated with the use of the system. Despite all attempts to mitigate the risks associated with the use of the system, it is possible that these events and other unanticipated events may occur. Though subjects may experience no benefit to participating in this study, the knowledge gained from the results and the application of that knowledge toward the future development of a stimulation system may benefit future patients and significantly improve the quality of life for patients suffering from

postoperative pain following TKA. The potential risks of participation in this study have been minimized such that they are unlikely to occur and/or have non-serious consequences. The knowledge gained from the study and the potential for temporary relief of pain justifies the minimal potential risk.

13.4 Risk Justification

[redacted]

14.0 Ethical Considerations

14.1 Declaration of Helsinki

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

14.2 Institutional Review Boards

It is the responsibility of the Principal Investigator to obtain and maintain written approval of the study protocol and the informed consent from the appropriate Institutional Review Board (IRB). It is further the Principal Investigator's responsibility to notify the IRB regarding any amendments/supplements to either the study protocol or the consent form. A copy of the written IRB approval, along with the approved versions of the consent and protocol, will be maintained in the study regulatory file. Written approvals will identify the study name and document the date of review.

In addition, a list of the IRB members and their titles will be obtained by the Investigator and maintained in the study regulatory files. Copies of both the IRB member list and the protocol and consent approvals will be furnished to SPR Therapeutics prior to any shipment of Investigational Devices.

14.3 Informed Consent Form

In accordance with 21 CFR 812, it is the responsibility of the Principal Investigator to give each participant (or the participant's legally authorized representative) full and adequate verbal and written information about the objectives of the study, the study procedures, and the potential risks of participating in the study prior to inclusion in the study. Potential study participants will be informed that their participation is voluntary and that they may withdraw their consent at any time and for any reason without sanction, penalty, or loss of benefits to which they are otherwise entitled. Potential participants will also be informed that withdrawal from the study will not jeopardize their future medical care. It is the Principal Investigator's responsibility to obtain a signed Informed Consent Form from each potential study participant prior to performing any study-related procedures and to document the informed consent process in the subject record.
The Informed Consent Form will be amended whenever new information becomes available that may be relevant to the subjects continued participation. Modifications to the Consent Form must be approved by SPR Therapeutics prior to submission to the IRB. The investigator must also inform SPR Therapeutics of any IRB mandated revisions to the study protocol.

14.4 Amending the Protocol

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

15.0 Study Administration

15.1 Record Retention

By signing the Investigator Agreement, the Investigator agrees to retain study-related documents in a secure location to which access can only be gained if required. Following study completion, the following documents will be archived: the study regulatory files containing all Good Clinical Practice (GCP) documents, including signed Informed Consent forms, patient-related materials, and CRFs. The Investigator will be required to retain all records required by this study during the investigation and for a period of 2 years after the later of the following two dates: The date of which the investigation is terminated or completed or, the date that the records are no longer required for purposes of supporting a pre-market approval application or a notice of completion of a product development protocol. The investigator must inform SPR Therapeutics if the location of the records changes or if there are any plans to destroy the records.

15.2 Criteria for Terminating the Study

SPR Therapeutics reserves the right to terminate the study at any time. SPR Therapeutics only intends to exercise this right for valid scientific or administrative reasons, and reasons related to the protection of Human Subjects participating in this study. Principal Investigators, IRBs, and the FDA will be notified in writing in the event of a study termination.

[redacted]

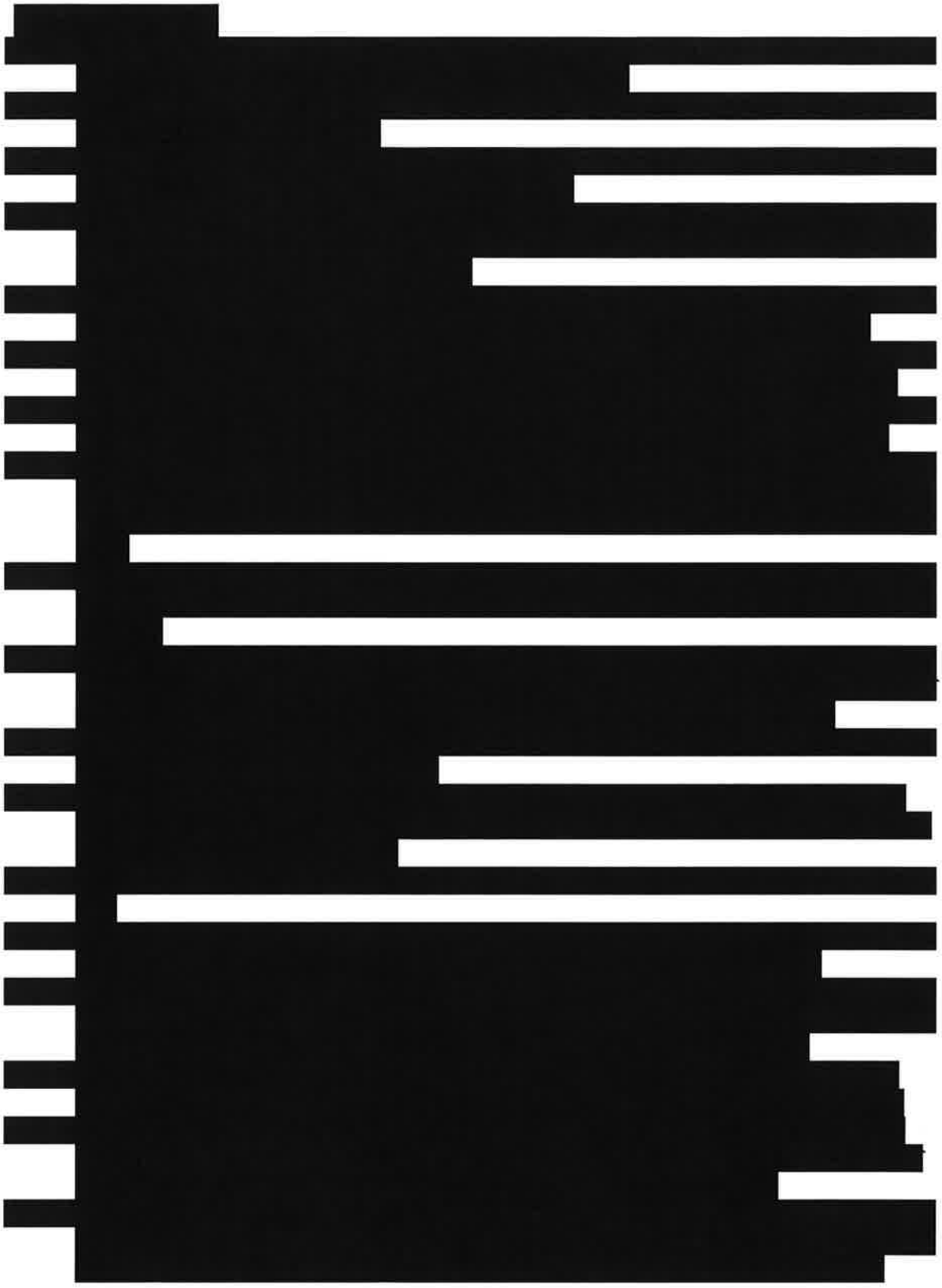
15.3 Criteria for Terminating a Center

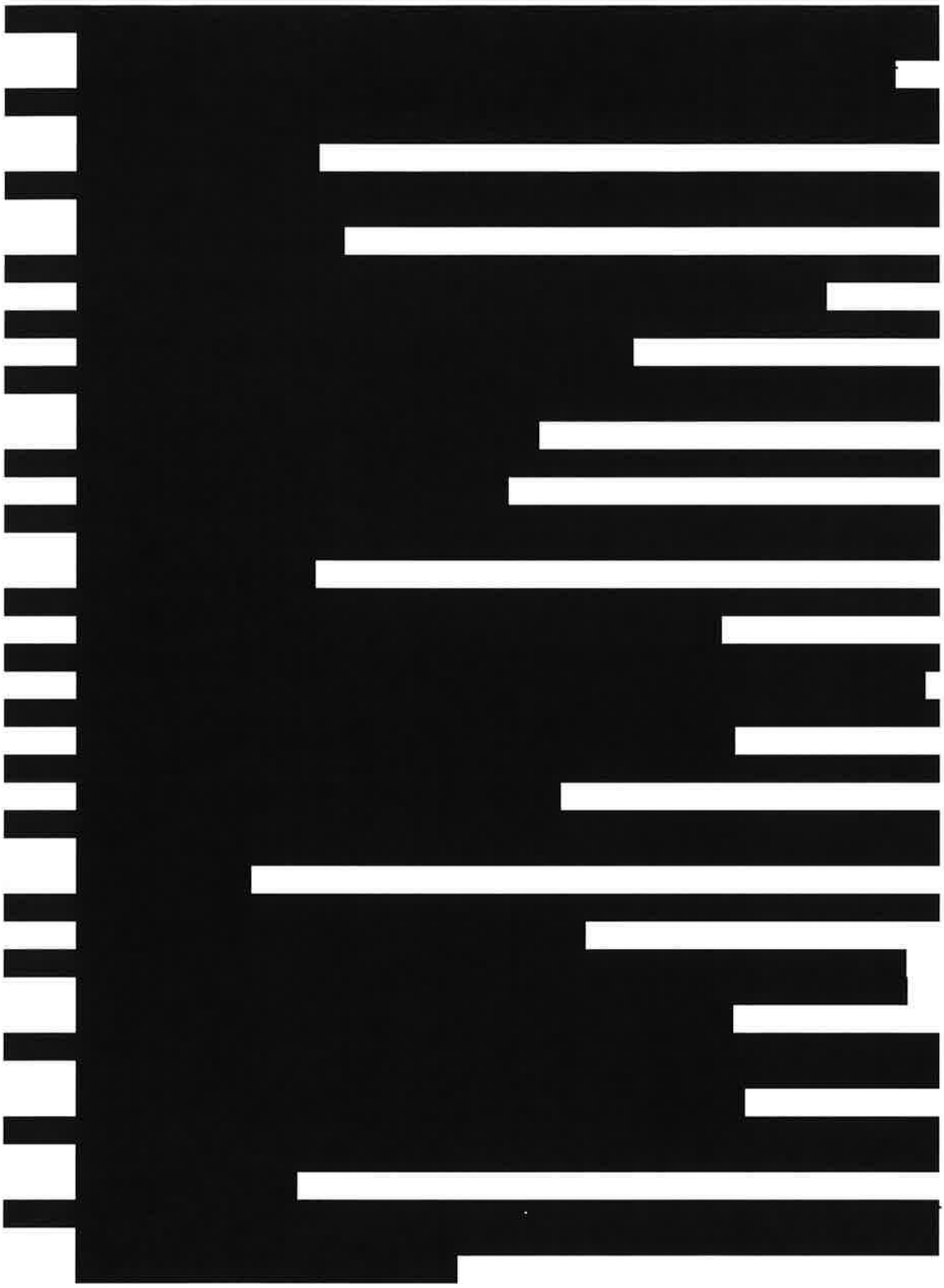
SPR Therapeutics reserves the right to suspend or stop the enrollment of subjects at a study center at any time after the study initiation if no subjects have been enrolled or if enrollment numbers are well below anticipated enrollment expectations. [redacted]

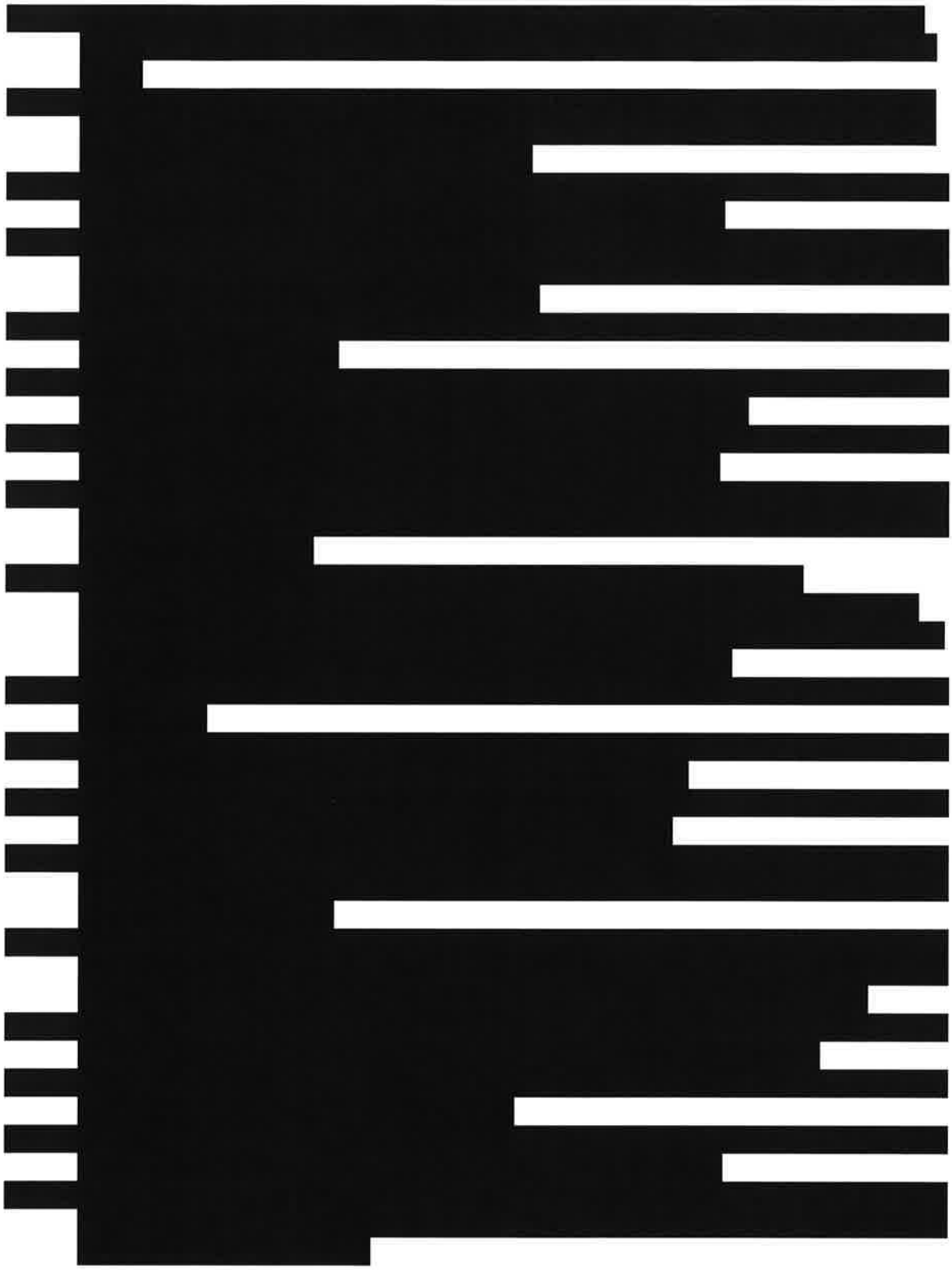
15.4 Investigator Qualifications/Responsibilities and Investigator Training

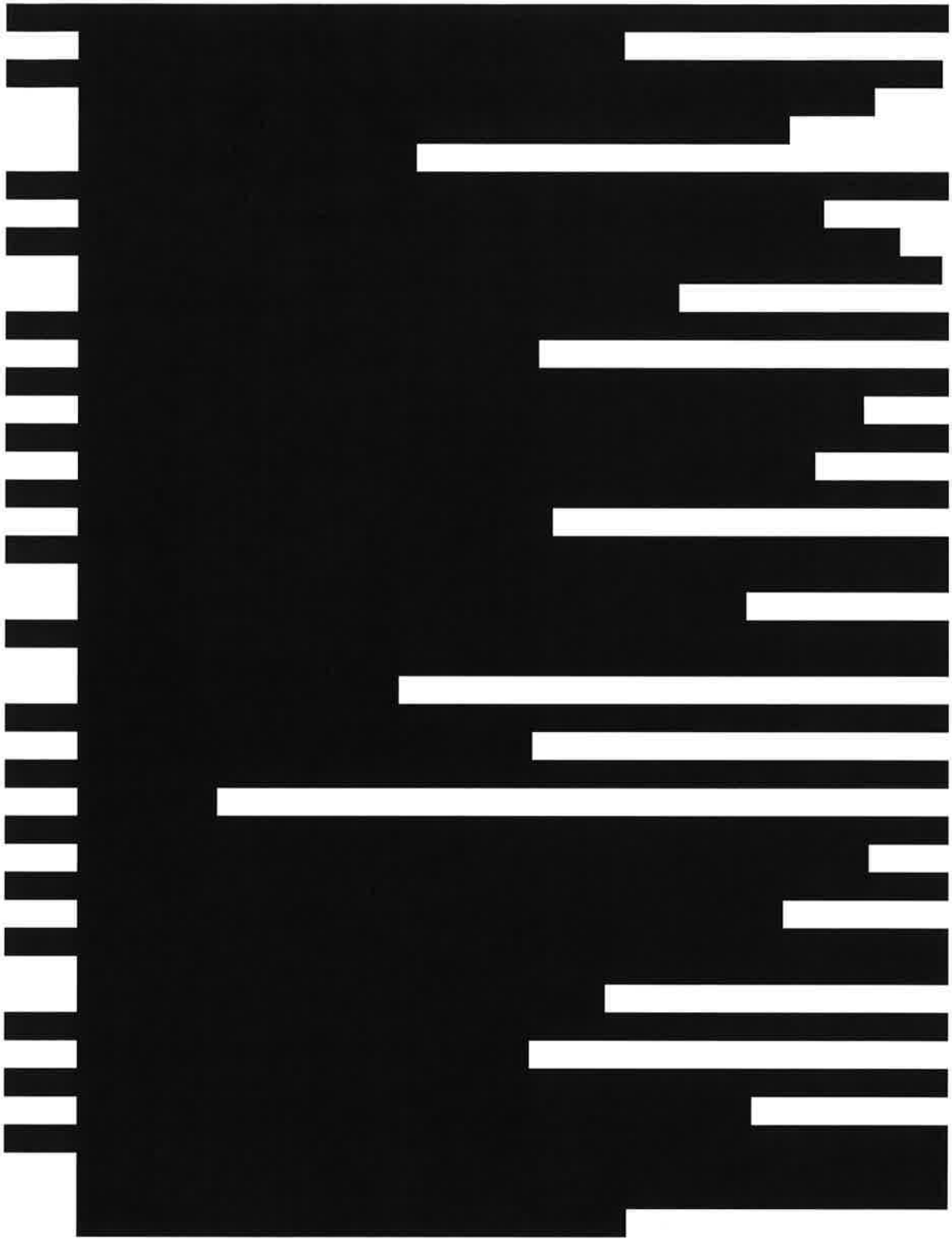
To participate in this study, the Investigator must sign the Investigator Agreement which documents his responsibilities in the study. The Investigator will require training on this study plan and the investigational device. [redacted]

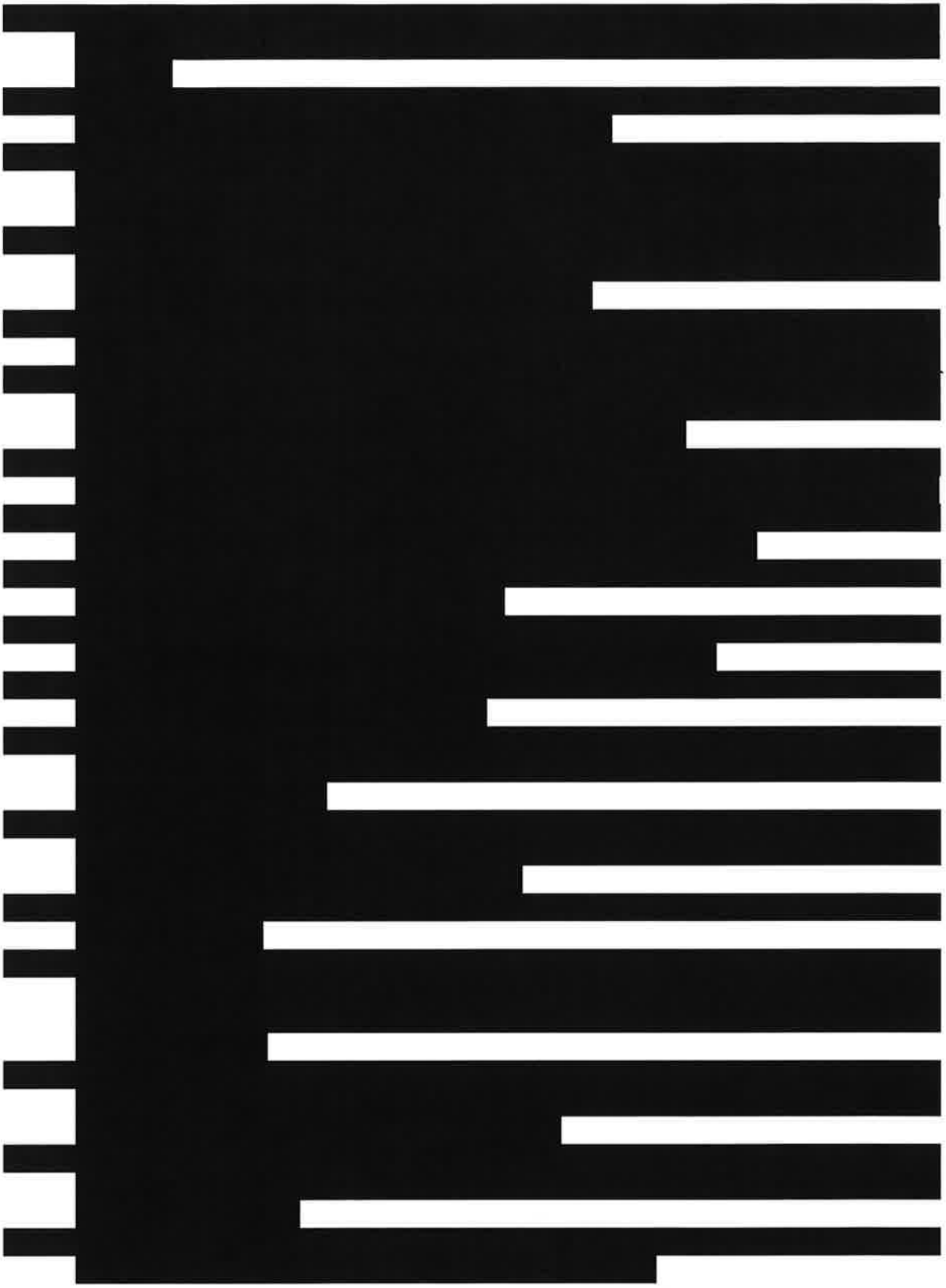
[redacted]

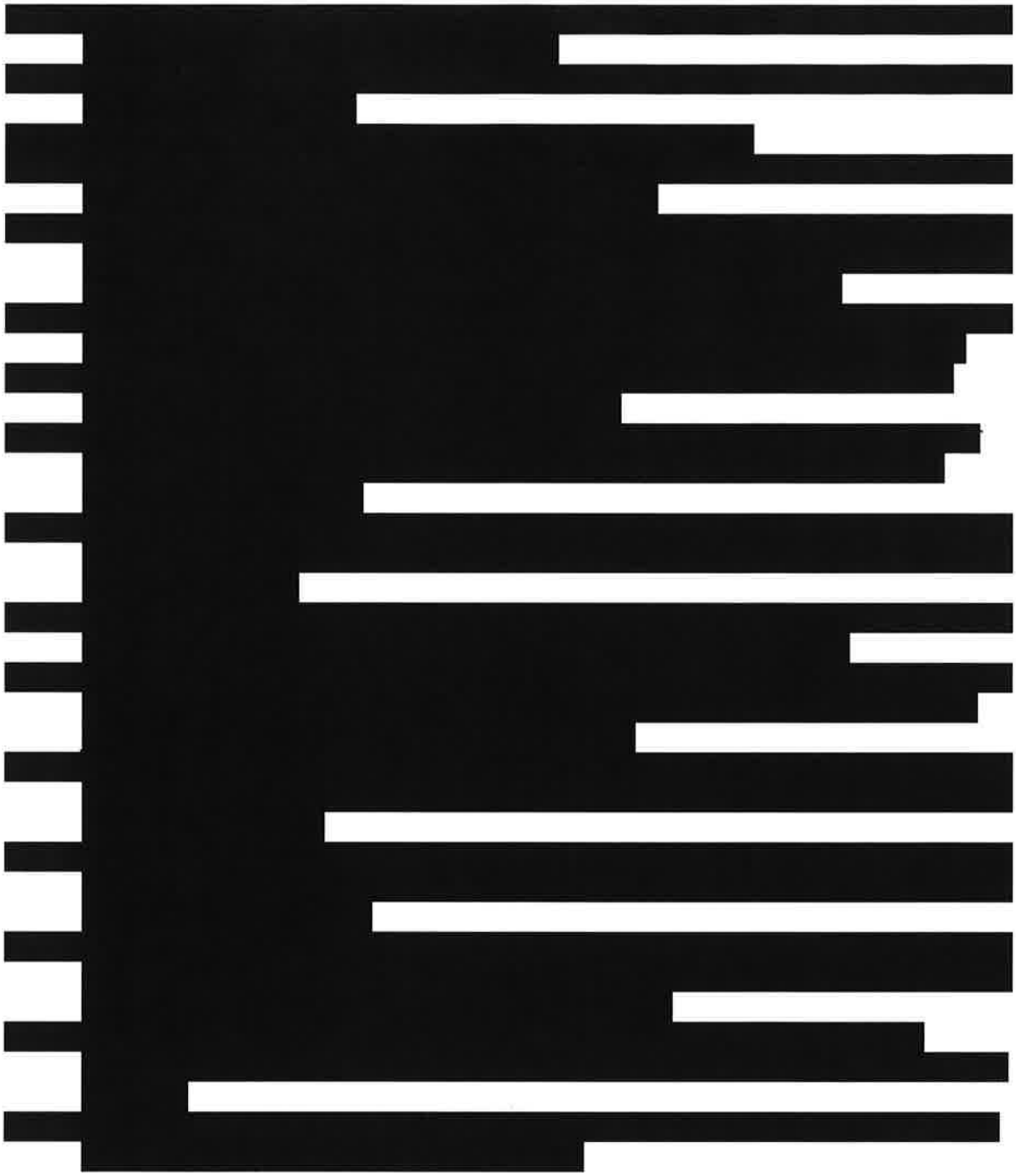












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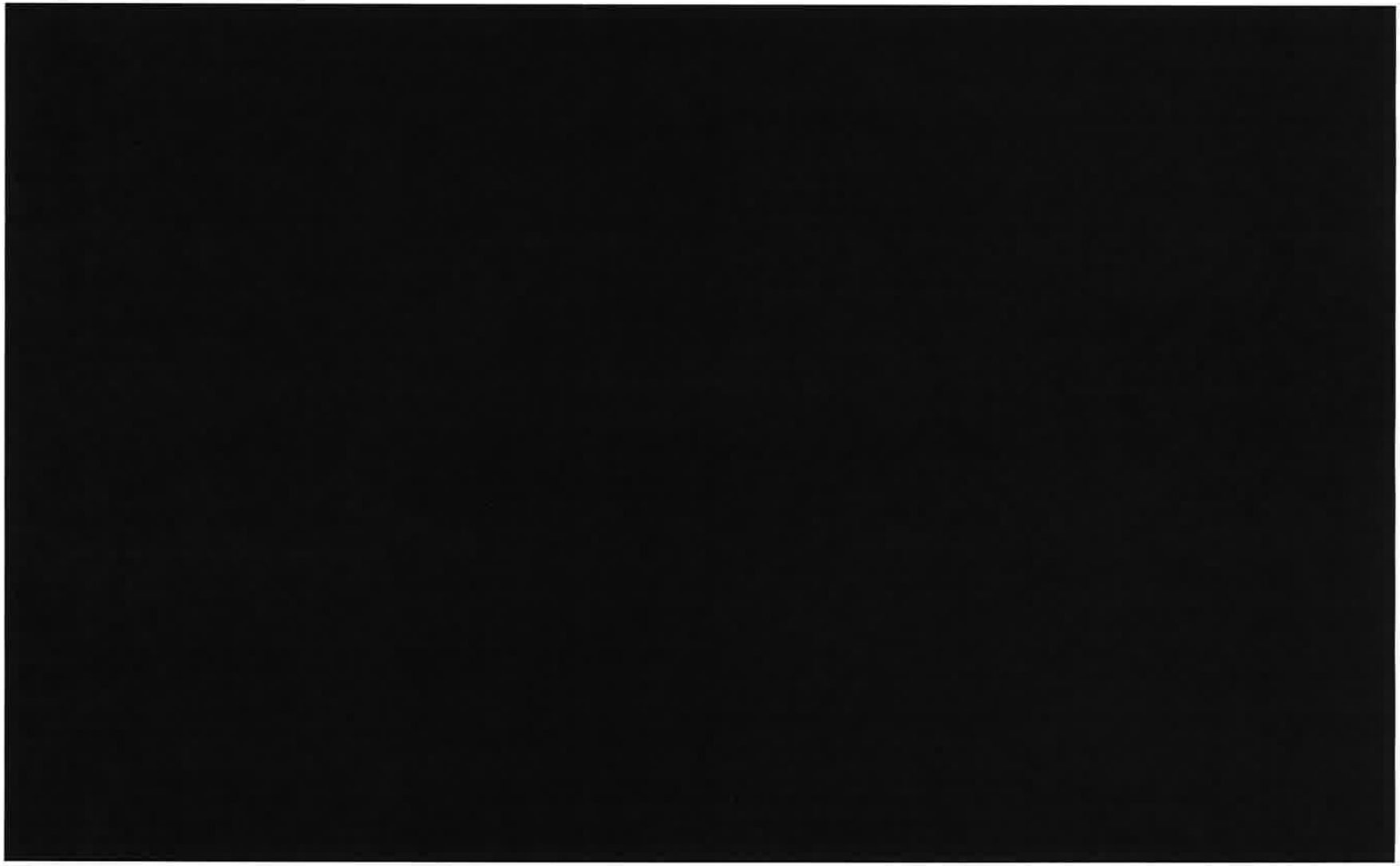

17.2 [redacted]

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