Clinical Study Protocol

Protocol Title:	A Prospective, Single-center, Pilot study in vivo lesion characteristics post Cooled Radiofrequency Denervation as Treatment for Chronic Pain.
Protocol #:	105-17-0004
Study Short Name:	MRI Exploration study
Country:	North America
Indications:	Pain Management; Chronic Pain that can be treated with Radiofrequency ablation.
Sponsor:	Mehul Desai, MD/Puneet Sayal, MD International Spine, Pain and Performance Center Washington, DC Site 2141 K Street, NW, Suite 600 Washington, DC 20037 Arlington, VA Site 1635 North George Mason Drive, Suite 180 Arlington, VA 22205 Attn: [Puneet Sayal] [202-808-8295]
Current Protocol Version:	V 2.0 24 May 2018
Initial Protocol Version:	V 1.0 17 January 2018

General Information

	Print	Signature
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1 Synopsis

Protocol Title:	A Prospective, Single-center, Pilot study to determine in vivo lesion characteristics post Cooled Radiofrequency Denervation
Test Article(s):	MRI characteristics of lesions post-radiofrequency ablation
Planned Number of Sites:	1
Planned Number of Subjects:	Up to 15
Study Design:	Prospective, Single-center, Human, Interventional
Study Duration:	**Individual Study Participation:** Up to 7 days post treatment
Objectives:	The primary objective of this protocol is to quantify CRFA lesion size on MRI post CRFA treatment.
Eligibility Criteria:	Inclusion Criteria 1. Age ≥ 21 years 2. Able to understand the informed consent form and provide written informed consent and able to complete outcome measures. 3. Must be clinically appropriate candidate to receive CRFA for treatment of chronic pain. 4. Willing and able to receive an MRI Exclusion Criteria 1. Unable to receive an MRI (i.e. due to pacemaker, iron-based metal implant, allergy to contrast medications utilized). 2. Extremely thin patients and those with minimal subcutaneous tissue thickness that would not accommodate a radiofrequency lesion of up to 14mm in diameter to limit the risk of skin burns. 3. Active joint infection or systemic or localized infection at the needle entry site (subject may be considered for inclusion once infection is resolved.) 4. Subject currently implanted with a pacemaker or defibrillator 5. In the event a pre-treatment MRI is obtained, trauma or injury occurring to the targeted area between the baseline MRI and CRFA treatment 6. Subject unwillingness or unable to comply with protocol requirements

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2 List of Abbreviations and Definition of Terms

Abbreviation	Definition
CRFA	Cooled Radiofrequency Ablation
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
PI	Principal Investigator
RF	Radiofrequency
SI	Sacroiliac
SIJ	Sacroiliac Joint

3 Introduction

3.1 Background / Study Population

Chronic back and hip pain is a leading cause of morbidity in an aging population. Sources of pain are highly variable and multiple treatment options exist including physical therapy, medications, injections, radiofrequency, PRP and ultimately surgery.

Cooled Radiofrequency ablation (CRFA) is a well-established method for delivering lesions into nervous tissue to accomplish neurotomy procedures. Multiple references exist in the literature noting the clinical outcomes of patients treated with CRFA cooled radiofrequency for pain managing denervation in other anatomic locations, including the sacroiliac joint[1,2,3,4], the lumbar spinal disc.[5,6,7] and recent human studies have started to demonstrate the effects of CRFA when specifically used for

genicular neurotomy procedures in patients with chronic knee pain resulting from conditions such as osteoarthritis[8].

3.2 RATIONALE FOR STUDY

This Prospective, Single-center, Pilot Study will assist in gaining an understanding of the actual CRFA lesions in an in vivo situation in areas where CRFA is utilized as a standard of care treatment option for the relief of chronic pain (cervical facet joints, thoracic facet joints, lumbar facet joints, Sacroiliac (SI) region, hip and knee). The primary rationale is to better quantify lesion properties in order to ensure procedural optimization. The study does not introduce any experimental procedures as the product will be used in a manner that is consistent with their labeled indications.

3.3 POTENTIAL RISKS & BENEFITS

Because radiation is not used, there is not risk of exposure to radiation during an MRI procedure. However, due to the use of the strong magnet, MRI cannot be performed on patients with:

- Implanted pacemakers
- Intracranial aneurysm clips
- Cochlear implants
- Certain prosthetic devices
- Implanted drug infusion pumps
- Neurostimulators
- Bone-growth stimulators
- Certain intrauterine contraceptive devices;
- Any other type of iron-based metal implants
- Allergies to contrast medications such as Gadolinium based contrast agents (GBCA) especially in patients with renal and/or kidney impairment.

MRI is also contraindicated in the presence of internal metallic objects such as bullets or shrapnel, as well as surgical clips, pins, plates, screws, metal sutures, or wire mesh. The use of GBCA is reason for serious concern with regards to the MRI procedure. Nephrogenic systemic fibrosis (NSF) has been linked to the use of GBCA in conjunction with MRI, specifically in patients with the following renal impairments:

- Acute Kidney injury

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- End-stage renal disease
- Stage 4 & 5 chronic kidney disease

Complications due to GBCA in renally impaired patients can manifest themselves in the following ways:

- Hyperpigmentation
- Yellow papules and/or plaques
- Blistering
- Ulceration

The results of such presentations include sever pruritus, paraesthesia, as well as pain, and flexion contractures that begin on the appendages and extend proximally[10].

If you are pregnant or suspect that you may be pregnant, you should notify your physician before receiving an MRI.

4 Study Objectives and Purpose

The primary objective of this protocol is to collect MRI data post CRFA treatment.

5 Investigational Plan

5.1 STUDY DESIGN

This study will be a prospective, single-center, pilot study. Adult subjects over the age 21 diagnosed with chronic joint pain (≥ 3 months), scheduled to receive Radiofrequency denervation and meet the selection criteria are eligible to participate in this study. The specific targeted areas of interest in this study will include Cervical facet joints, Thoracic facet joints, Lumbar facet joints, Sacroiliac (SI) region, hip and knee.

The treating physician will follow Standard of Care treatment for all enrolled subjects. As illustrated in Figure 1, the study consists of a screening visit, a treatment visit and a follow up visit. All subjects receiving CRFA will receive an MRI 2 – 7 days after the CRFA procedure. Subjects receiving CRFA of the Sacroiliac Joint will also receive an MRI within 30 days prior to the CRFA procedure. The treating physician may also request an MRI be performed prior to the procedure for subjects receiving CRFA of other targeted areas. The point of enrollment for each subject is the time that they sign the Informed Consent Form.

MRI data will be reviewed by the radiologist on a per patient basis to confirm lesion characteristics. It is anticipated that 3-5 subjects per level will be needed to fully quantify lesion characteristics, however; enrollment will remain flexible for each targeted area based on real time review of MRI data.

Figure 1: Study Design

CRFA = Cooled Radiofrequency Ablation procedure

5.2 ENDPOINTS

5.2.1 PRIMARY ENDPOINT

Quantifiable MRI data of CRFA lesion.

5.3 MEASURES TO MINIMIZE / AVOID BIAS

An independent radiologist will review MRI data, Dr. Yair Safriel.

5.4 DURATION OF SUBJECT PARTICIPATION

The screening period could take up to 30 days to complete for all subjects. Subjects will participate in the study through receipt of their MRI (approximately 10 days from the time of the procedure).

5.5 STUDY-STOPPING CRITERIA

Post procedure MRI for each targeted area will be reviewed in real time. This will allow for analysis of the MRI by modality. Each targeted area will be reviewed independently and collectively and the study may be terminated at any time once MRI data collected is adequate to quantify lesion characteristics. Additionally, enrollment adjustments may be made for each area independently based on information received.

The study may also be terminated if the sponsor determines that there is a clinical or other reason to do so. In the event the study is stopped, subjects already enrolled will be followed according to the protocol and recruitment will be stopped. Potential reasons for early termination may include (but are not limited to):

- Stopping for success following interim analysis
- Stopping for futility following interim analysis
- Administrative reasons

5.6 TREATMENT ASSIGNMENT / RANDOMIZATION

There is no randomization performed in this study. All eligible and enrolled subjects will receive Radiofrequency Treatment per Standard of Care. The MRIs will be conducted per standard of care within the windows detailed in this protocol.

6 Subject Selection

Subjects will include individuals who are scheduled to receive Cooled RF treatment as part of their Standard of Care for their condition/disease state. Subjects will be required to sign informed consent for the MRI and to allow data to be utilized for research.

6.1 INCLUSION CRITERIA:

1. Age ≥ 21 years
2. Able to understand the informed consent form and provide written informed consent and able to complete outcome measures.
3. Must be clinically appropriate candidate to receive CRFA for treatment of chronic pain.
4. Willing and able to receive an MRI

6.2 EXCLUSION CRITERIA:

1. Unable to receive an MRI (i.e. due to pacemaker, iron-based metal implant or allergies to contrast medications utilized).
2. Extremely thin patients and those with minimal subcutaneous tissue thickness that would not accommodate a radiofrequency lesion of up to 14mm in diameter to limit the risk of skin burns.
3. Active joint infection or systemic or localized infection at the needle entry site (subject may be considered for inclusion once infection is resolved.)
4. Subject currently implanted with a pacemaker or defibrillator

5. In the event a pre-treatment MRI is obtained; trauma or injury occurring to the targeted area between the baseline MRI and CRFA treatment
6. Subject unwillingness or unable to comply with protocol requirements

7 Study Procedures

7.1 CENTER READINESS

Prior to initiating study procedures, all applicable regulatory requirements must be fulfilled. Each study site must have written documentation of readiness including but not limited to:

- Investigational Review Board (IRB) approval of the current version of the Clinical Investigation Plan (Protocol) and Informed Consent Form (ICF) or waiver obtained indicating IRB oversight is not required
- Signed/dated Curriculum Vitae and current medical licensure for Investigator and Sub-Investigator(s)
- Signed/dated Financial Disclosure Forms for Investigator and Sub-Investigator(s)

7.2 INFORMED CONSENT PROCEDURES

Prior to undergoing any study procedure or baseline testing, each subject must indicate their consent by signing and dating the current IRB-approved Informed Consent Form. Consent forms must be approved by the IRB prior to implementation and must be provided to the subject in their primary language complying with the requirements of 21 CFR 50.

Adequate time should be provided for subjects and/or legally authorized representatives (LARs) to review the consent form and ask any questions. The subject should receive a copy of the signed/dated consent form for their records. Information detailing the Informed Consent process must be clearly documented in each subject's medical/study record (source document).

7.3 MEASURES AND METHODS OF ASSESSMENT

The following assessments will be utilized throughout the study in accordance with the assessment schedules described below.

7.3.1 SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

	V1	V2	V3
	Screening	**Index Procedure / Treatment (DAY = 0)**	**MRI Procedure**
	Within 30 Days of ICF	**Within 30 Days of Screening**	**2-7 days post treatment**
Informed Consent	X		
Inclusion/Exclusion	X	X	
(CRFA) Applications		X	
MRI (SI patients only)	X		X

7.3.2 DEMOGRAPHIC INFORMATION

Age, gender, race, BMI, treatment history, comorbidities, and concomitant medications will be collected for demographic analysis.

7.3.3 MRI INFORMATION

Ideal conditions for MRI are described below:

- RF entry points should be marked on the scan with MRI compatible markers at the time of scan.
- All axial images should be a stack (not angled to disc or any other structures).
- All slices should be 3mm thick with a gap of no more than 0.3mm through the area of RF.
- Post contrast imaging would be ideal.
- Axial and sagittal post contrast T1 fat suppressed (Dixon suppression, if possible on all subjects)
- T2 based imaging should be both axial and sagittal. Ideally, preference towards T2 fat suppression/T2FS (Dixon suppression, if possible on all subjects) in both planes.
- Should have STIR on all studies as well in both planes.
- If time/cost does not permit both T2FSand STIR, default to STIR only. If no post contrast imaging, should really have both STIR and T2FS.

8 Procedures by Visit

8.1 Visit 1 - Screening

1. Perform standard of care work up to ensure potential patient is an appropriate candidate to receive CRFA in one of the targeted areas identified within this study
2. Subject Selection / Informed Consent
3. Schedule and Perform MRI of treatment area (if applicable)
4. Schedule Treatment visit within 30 days of ICF

8.2 Visit 2 - Index Treatment (Day 0)

1. Verify that subject continues to meet all eligibility criteria.
2. Perform CRFA procedure per standard of care

8.3 Visit 3 - (2-7 days post procedure)

1. Perform MRI of treatment area.

8.4 Discontinuation / Early Termination (ET)

Subjects may withdraw from the study at any time for any reason. Early terminations can occur under the following circumstances:

1. Subject Withdraws Consent
2. Investigator withdraws the subject for any reason following discussion with the sponsor
3. Investigator withdraws the subject immediately for emergent safety issue and reverts to institutional standards-of-care
4. Subject becomes Lost-to-Follow up (LTF)

The study may be terminated by the investigator at any time for any reason. This could include the situation where consistency in lesion characteristics is identified across treatment areas. If a subject is withdrawn or the study is terminated, investigators will continue to treat per institutional standard of care procedures.

9 Adverse Event Reporting

9.1 ADVERSE EVENTS (AE) ASSESSMENT

Adverse Events will be managed and treated per Standard of Care.

10 Statistical Methods and Data Analysis

Data collected within this protocol will be reported utilizing descriptive statistics.

10.1 STUDY SUBJECTS

Sample size requirements are estimated and depending on quality of imaging returned, fewer patients may be needed within each targeted area. Image analysis will happen in real time in an effort to confirm when sufficient data exists for each targeted area. Additionally, if consistency in lesion characteristics is identified across treatment areas, the study could be stopped before estimated enrollment is complete.

10.2 PRIMARY EFFICACY PARAMETERS

MRI imaging review containing the ability to quantify the lesion being created.

10.3 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND CONCOMITANT MEDICATIONS

Demographic data, medical history, and concomitant medications will be summarized by means of descriptive statistics (number, mean, SD, median, minimum, and maximum) or frequency tables.

10.4 EFFICACY ANALYSES (MAY BE CHANGED AS NEEDED FOR CONSUMER STUDIES)

10.4.1 PRIMARY EFFICACY ANALYSIS

No efficacy analyses will be performed in this study.

11 Ethical, Administrative, and Regulatory Obligations

11.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The study protocol, ICF document(s), and any amendments must be submitted to and approved by the IRB/IEC prior to enrolling subjects. The IRB must be operating in compliance with 21CFR Part 56.

11.2 HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT (HIPAA)

In accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996, the Investigator must obtain authorization from the patient to use and/or disclose protected health information (PHI). HIPAA authorization may be obtained as part of the ICF or in a separate document. HIPAA authorization must include:

A. Identification of the parties that can use and disclose the PHI
B. Identification of the parties to whom the PHI may be disclosed

C. A meaningful description of the PHI
D. A description of each purpose for the use and disclosure
E. Information about the subject's rights related to the authorization
F. Information about the expiration of the authorization
G. Instructions on how to revoke the authorization
H. A statement about what may happen if the authorization is not signed
I. A warning that once information has been released, it may be released again without further authorization

12 Records Retention and Archival

Study records must be maintained per requirements outlined in 21 CFR 812.140.

13 References

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5 Kapural L, Mekhail N. Novel intradiscal biacuplasty (IDB) for the treatment of lumbar discogenic pain. Pain Pract 2007 Jun; 7(2):130-4.

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