Title:	Five-Plus Year Follow-Up of SMART (**S**urgical **M**ulti-center **A**ssessment of **R**F Ablation for the **T**reatment of Vertebrogenic Back Pain) Trial
Protocol Number:	**CIP 0011, Rev. A**
Device:	**INTRACEPT® INTRAOSSEOUS NERVE ABLATION SYSTEM**
Regulatory Status:	The device has FDA 510(k) clearance in the US and is CE marked in the EU for its intended purpose as defined in the Instructions for Use
Sponsor:	Relievant Medsystems 8500 Normandale Lake Blvd., Suite 2150 Minneapolis, MN 55437
Date:	**April 5, 2019**

CONFIDENTIAL

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1 SYNOPSIS

Protocol Title:	Five-Plus Year Follow-up to SMART (**S**urgical **M**ulti-center **A**ssessment of **R**F Ablation for the **T**reatment of Vertebrogenic Back Pain) Trial
Protocol Number:	CIP 0011, Rev A
Sponsor:	Relievant Medsystems, Inc.
Objectives	The objective of this study is to evaluate long-term ongoing effectiveness of the Intracept® Intraosseous Nerve Ablation System for the treatment of chronic low back pain.
Regulatory Status	The Intracept® Intraosseous Nerve Ablation System is FDA 510(k) cleared and CE Marked for the ablation of basivertebral nerves of the L3 through S1 vertebrae for the relief of chronic low back pain of at least 6 months' duration that has not responded to at least 6 months of conservative care, and is also accompanied by either Type 1 or Type 2 Modic changes on magnetic resonance imaging (MRI).
Study Design	This is a prospective multi-center, noninterventional, observational post market data collection of the 5+ year effectiveness and satisfaction outcomes for the SMART trial population.
Number of Subjects	133 (subjects treated in original SMART protocol in the US)
Number of Sites	13 sites in the US
Duration of Participation	Subjects will be asked to complete one telephone study visit. It is estimated that this study will take approximately 6 months to re-contact the subjects and perform the study visit.
Efficacy Assessments	Pain, disability, satisfaction, and interventions, using the following measurements: • Oswestry Disability Index (ODI)-based questionnaire interview • Low back pain numeric rating (Scale 0 to 10) • Injections in last 12 months • Lower back interventions (since Intracept procedure) • Narcotics in last 30 days • Satisfaction survey

2 INTRODUCTION

Recent studies have demonstrated that vertebrogenic pain from degenerated or damaged vertebral endplates is an important source of chronic low back pain (CLBP).[1-6] Vertebal endplate damage can lead to cellular communication between the disc nucleus and the bone marrow, triggering inflammation in the intraosseous space.[4] The basivertebral nerve (BVN) within the vertebral disc has nociceptors that receive pain signals from the damaged and inflamed endplate and transmit these pain signals to the central nervous system. Endplate damage and inflammation of the intraosseous space are visible as Modic changes on Magnetic Resonance Imaging (MRI).[4]

The Intracept device is a minimally-invasive intervention using a transpedicular approach to deliver radiofrequency (RF) energy to ablate the BVN. Once ablated, these nerves no longer transmit pain signals. The Intracept® Intraosseous Nerve Ablation System is FDA 510(k) cleared and CE Marked for the ablation of basivertebral nerves of the L3 through S1 vertebrae for the relief of chronic low back pain of at least 6 months' duration that has not responded to at least 6 months of conservative care, and is also accompanied by either Type 1 or Type 2 Modic changes on magnetic resonance imaging (MRI).

Following a successful pilot study[7], a 2:1 randomized, double-blind, sham-controlled trial demonstrated the safety and efficacy of intraosseous RF ablation of the BVN to treat CLBP in patients with Modic type 1 or 2 changes of the vertebral endplates. The SMART trial was conducted between 2011 to 2014 and enrolled 225 subjects at 15 sites (N=202) in the United States and 3 sites (N=23) in Europe.[8] The primary requirements for inclusion in the trial were CLBP with a duration greater than 6 months; CLBP non-responsive to at least 6 months of non-surgical management; and Modic Type 1 or 2 changes at the vertebral endplates of the levels targeted for treatment.

The primary efficacy endpoint for the original study was the 3-month change in Oswestry Disability Index (ODI) compared between the study arms. This comparison, as previously reported,[8] found that at 3 months the per-protocol (PP) treatment group exhibited a 20.5 Least Squares Mean (LSM) improvement in ODI compared to a 15.2 LSM improvement in the sham group ($p = 0.019$). The PP treatment arm subjects exhibited a durable ODI mean improvement (23.4 points) at 24 months.[9] In terms of percent improvement in ODI from baseline, these results translate into mean percentage improvements of 46.2% at 12 months and 53.7% at 24 months. Responder rates for ODI and low back pain visual analogue scale (VAS) were also maintained through two years, with patients showing clinically meaningful improvements in both: ODI ≥ 10-point improvement in 76.4 percent of patients and ODI ≥ 20-point improvement in 57.5 percent; VAS ≥ 1.5 cm improvement in 70.2 percent of patients. Patients receiving the Intracept Procedure also decreased utilization of opioids and spinal injections as compared to utilization prior to treatment.

The purpose of this study is to measure the 5+ year effectiveness outcomes in subjects treated with the Intracept Procedure in this original SMART study population.

3 STUDY DESIGN

3.1 Overview

The SMART 5-Year study is a prospective multi-center, noninterventional, observational post market data collection of the 5+ year effectiveness and satisfaction outcomes for the SMART trial treatment arm population. This trial will be conducted according to Good Clinical Practice (GCP) guidelines, including informed consent and Independent Review Board (IRB) approval and oversight.

3.2 Objective

To evaluate the 5+ year effectiveness outcomes of the Intracept Procedure for the relief of CLBP in the SMART trial treatment arm subjects.

3.3 Scope and Study Population

This study is a post-market, non-interventional, data collection of the 5+ year follow-up in the 133 treated subjects in the SMART trial in the U.S. The study will be conducted at the same thirteen U.S. study sites where the procedures occurred. U.S. subjects who were randomized to the treatment arm of the original SMART trial are eligible to participate in this 5+ year follow-up data collection.

3.4 Study Duration

Participants in the study will have a single study visit. Participants will be consented and then evaluated via a single telephone study visit.

4 PROTOCOL

This study entails contacting original SMART trial treatment arm subjects to seek participation in a data collection of current pain, functional status, and recent treatments. The study will be overseen at each participating study site by a primary investigator and clinical research coordinator (CRC). Telephone visits and data collection will conducted by an independent study-wide clinical research nurse (CRN).

Five-Plus Year Follow-up Visit

Study subjects who were randomized to the treatment arm and received treatment in the original SMART trial are eligible to participate in this 5+ year follow-up data collection. Each study site will make initial contact with the prior study patient and discuss the SMART 5+ year data collection and discern if the prior subject is interested in participating. Informed consent will be obtained, and the same unique subject ID # used in the SMART trial will be assigned to the subject. Study participant logs will include subject ID, date(s) of contact, and date of consent/decline to participate and will be maintained by the study site and independent CRN.

Upon subject agreement to participate in the study, the CRC will forward subject contact information to the independent CRN who will then ensure informed consent and schedule the telephone study visit. The independent CRN will perform the telephone study visit and will be responsible for collection of all data elements on source document worksheets

including administering a verbal ODI-based questionnaire, collecting a numeric rating of low back pain over the past 7 days, an assessment of narcotic medications for low back pain taken in the past 30 days, injections for low back pain in the last 12 months, and surgical interventions since the subject's Intracept Procedure, and patient satisfaction with the Intracept Procedure. The independent CRN will enter all data elements into the clinical database.

5 ENDPOINTS

5.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is the mean improvement in ODI from baseline to 5+ years.

5.2 Secondary Effectiveness Endpoint

Secondary effectiveness endpoints are:

a) The mean reduction from baseline in patient reported pain.

b) Responder rates for ODI - proportion of subjects who achieve ≥ 10-point reduction in ODI from baseline to 5+ years post-treatment.

c) Responder rates for pain rating - proportion of subjects who achieve a ≥ 1.5-point reduction in pain rating from baseline to 5+ years post-treatment.

d) The proportion of patients with surgical interventions for low back pain of the same treatment region post the Intracept procedure.

e) The proportion of patients currently utilizing opioids for low back pain of the same treatment region.

f) The proportion of patients utilizing injections in the past 12 months for low back pain of the same treatment region.

g) Patient satisfaction with the Intracept Procedure.

6 STATISTICAL ANALYSIS

6.1 Statistical Methods

Demographic and baseline characteristics will be summarized using descriptive statistics.

The mean change from baseline to five years in the ODI is the primary endpoint for this study. Statistical differences will be tested using Student's t-test. An analysis of covariance will also be performed using baseline characteristics and ODI measurments.

Secondary endpoints will be summarized using descriptive statistics.

- Mean reduction in pain rating baseline to 5+ years.
- Responder rates for ODI will be determined by the proportion of subjects who achieve ≥ 10-point reduction in ODI from baseline to 5+ years post-treatment.
- Responder rates for pain rating will be determined by the proportion of subjects who achieve a ≥ 1.5-point reduction in pain rating from baseline to 5+ years post-treatment.

- Number and rate of surgical interventions post-procedure, as adjudicated by an independent reviewer.
- The proportion of patients currently utilizing opioids for low back pain of the same treatment region.
- The proportion of patients utilizing injections in the past 12 months for low back pain of the same treatment region.
- Patient satisfaction with the Intracept Procedure at 5+ years.

No imputations will be made for missing data.

7 DESCRIPTION OF STUDY ASSESSMENTS

7.1 Oswestry Disability Index

The Oswestry Disability Index (ODI) is a validated questionnaire of low back pain-related disability.[10] It assesses the impact of low back pain on activities of daily living and participation and includes 10 questions. It is scored on a scale of 0 (no disability) to 100 (complete disability), with categories of 0-20 (minimal disability), 21-40 (moderate disability), 41-60 (severe disability), 61-80 (crippling back pain), and 81-100 (bed-bound or exaggerating). The minimally clinically important difference for this tool is considered to be 10 points.[11]. For the purposes of this study, this will be administered over the phone.

7.2 Pain Rating Scale for Back Pain Assessment

The pain rating scale that will be used for this study is a 10-point numeric scale based on the Visual Analogue Scale (VAS) pain rating questionnaire[12] used during the SMART study, 0 being no pain and 10 being worst imaginable pain. Respondents are asked to indicate what integer on the scale corresponds to their perceived level of pain in their low back. Subjects will be specifically instructed to report their level of low back pain as an average for the last seven days. Studies have shown that a minimally clinically important difference in VAS is considered to be approximately 1.5 points.[13] For the purposes of this study, this will be administered over the phone.

7.3 Patient Satisfaction

Satisfaction will be assessed with a short, non-validated questionnaire about degree of improvement, satisfaction with treatment, and willingness to repeat the treatment for the same outcome.

7.4 Narcotic Medications & Injections

Patient-reported low back narcotic usage will be captured at the 5+ year follow up visit. Drug type, prescribed dosage, and average daily dose for the last 30 days will be documented on the source document worksheet.

Patient-reported injections within the last 12 months will be collected. Date, type, and location for each injection will be recorded.

7.5 Surgical Interventions

Surgical interventions performed since the Intracept Procedure will be captured. Date, type and location of each intervention will be recorded.

Interventions will be adjudicated by an independent reviewer.

8 STUDY RISK ANALYSIS

This study is categorized as a non-significant risk study with minimal risk to subjects. The primary risk to study participants is a loss of confidentiality. This risk will be mitigated through assignment of the unique Subject ID # and de-identification of data. Subject contact information will only be utilized by authorized independent CRNs (under patient consent) for purposes of conducting the study visit.

There is no additional benefit to the study subjects for participating in the study. There may be benefit to participants and future patients to learn about the long-term treatment effect of the Intracept Procedure.

9 IRB APPROVAL, INFORMED CONSENT, DATA COLLECTION, DATA HANDLING, AND RECORD KEEPING

9.1 Institutional Review Board (IRB) Approval

This study will be conducted under IRB review and approval of the protocol, the informed consent document/process, subject stipend, and study materials before the start of the study.

9.2 Informed Consent

Informed consent shall be obtained and documented before a subject is scheduled for the follow-up telephone visit. It is the responsibility of the investigator/independent CRN to ensure that informed consent is obtained from the subject and documented before any study follow-up activity is undertaken.

9.3 Confidentiality

Subject medical information obtained for this study is confidential, and disclosure to third parties other than those authorized for the study and IRB/regulatory oversight is prohibited. Subjects will be only identified by the unique study number that the subject used during the SMART study. Data will be de-identified in a manner compliant with HIPAA regulations.

Upon the subject's agreement to participate, the independent CRN will schedule and conduct the telephone study visit. Subject's permission for the use of records for supplemental data and data verification purposes will be obtained prior to accessing subject's medical records.

Data generated by this study must be available for inspection upon request by representatives of the FDA, national and local health authorities, the Sponsor or its designee, and the IRB for the study site, if appropriate.

9.4 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data for this study is the patient-reported outcomes recorded on the source document worksheets, which will serve as the primary data collection instrument for the study. A designated independent CRN will be responsible for conducting the 5+ year telephone visit, collecting the requested data at the visit, and for the timely completion and submission of data into the clinical database. A clinical database will be used to store patient-reported questionnaire responses. Investigators will maintain all supporting medical records, and the independent CRN will maintain Informed Consent Forms and/or documentation of informed consent.

9.5 Regulatory Compliance

The Intracept System received FDA 510(k) clearance in 2016 for the Indications for Use being studied under this protocol. This study will be conducted in compliance to applicable regulations contained in 21 CFR 11, 50, and 56, as well as the ICH/GCP Guidelines. The investigator and all research staff participating in this study are expected to adhere to this protocol, applicable privacy laws, and any approval requirements imposed by the Institutional Review Board. The investigator has the further responsibility of adherence to the Investigator Agreement and to maintain the contents of the Regulatory Binder.

9.6 Data Quality Assurance

Steps to assure the accuracy and reliability of data include the selection of a qualified clinical investigator, site research personnel, and the study-wide independent CRN. Investigators and study personal will be trained on the protocol and study procedures prior to the study. The Sponsor and/or its delegate will review data accuracy and completeness during and after the study, and any discrepancies will be resolved with the clinical investigator or designee as appropriate.

The Sponsor has designed quality assurance procedures to ensure complete, accurate and timely data are collected and the study protocol requirements are followed. In addition to GCP and internal standard operating procedures, the SMART Trial 5+ year follow-up study will utilize the following procedures to further ensure quality:

- Quality control of data submitted will be done by Sponsor, and any data problems will be addressed with the study site and or independent CRN.
- All source worksheets and data files will be secured to ensure confidentiality.
- The Sponsor will maintain regular contact with each study site and the independent CRN as needed to evaluate protocol compliance and/or to verify the study site facilities continue to be adequate.
- The site will permit study-related audits and inspections by the IRB, the Sponsor and government regulatory bodies of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.).
- Each Investigator is required to execute a Clinical Trial Agreement which delineates their responsibilities as an investigator.

9.7 Record Retention

It is the Investigator's responsibility to retain study essential documents for at least 2 years after completion of the study.

10 STUDY FUNDING, SUBJECT STIPENDS, AND CONFLICTS OF INTEREST

Funding for study-related informed consent and the telephone follow-up visit is provided by Relievant Medsystems. Relievant Medsystems maintains policies to ensure compliance with the financial regulations for clinical studies.

Subjects will be reimbursed reasonable costs for their time to perform the 5+ year telephone follow-up study visit. Upon completion of the telephone study visit, the subject will be issued a stipend card.

Patient payments will be made as directed in the Clinical Trial Agreement. The amount of stipend and conditions for payment to the subject will be outlined in the informed consent form and must be approved by the IRB.

11 PUBLICATION POLICY

The results of this trial will be reported regardless of whether the outcome is in favor of the trial interventions. The Sponsor retains the right to review any submitted publications for accuracy prior to submission. Authorship of manuscripts will be based on International Journal Editors' guidelines for authorship.

12 REFERENCES

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13. APPENDIX 1: INVESTIGATOR SIGNATURE PAGE

Title: **Five-Plus Year Follow-Up of SMART (Surgical Multi-center Assessment of RF Ablation for the Treatment of Vertebrogenic Back Pain) Trial**

Protocol Number: **CIP 0011, Rev. A**

Date: **April 5, 2019**

I have received and read the protocol listed above. I agree to undertake the protocol as defined therein and in accordance with the relevant parts of the 21 CRF 50 Protection of Human Subjects, ICH Guidelines for GCP, ISO 14155, the Declaration of Helsinki, and any other pertinent individual country laws/regulations. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form must first be approved by the Sponsor and the Institutional Review Board, except those changes necessary to eliminate apparent immediate hazards to patients, or purely administrative changes, which must first be approved by the Sponsor. Failure to adhere to these stipulations may constitute a breach of United States Federal Regulations and may result in my termination of the study.

Principal Investigator (Print Name) _____

Principal Investigator (Signature) _____

Date: _____