# Multi-Center Evaluation of Clinical Outcomes of Pulse Widths <500$\mu$sec and >1000$\mu$sec During a Temporary Spinal Cord Stimulation Trial

| | |
|---|---|
| **Title:** | **Multi-Center Evaluation of Clinical Outcomes of Pulse Widths <500$\mu$sec and >1000$\mu$sec During a Temporary Spinal Cord Stimulation Trial** |
| **Protocol Number:** | TBD |
| **Device:** | Nuvectra® Algovita® Spinal Cord Stimulation System |
| **Sponsor:** | The Ohio Pain Clinic<br>7076 Corporate Way<br>Dayton, OH 45458 |
| **Sponsor Contact:** | Amol Soin, MD<br>7076 Corporate Way<br>Dayton, OH 45458<br>drsoin@gmail.com |
| **Study Sites:** | TBD |
| **Medical Monitor:** | Erin Dewenter, RN<br>Ohio Pain Clinic<br>7076 Corporate Way<br>Dayton, OH 45458 |
| **Date of Protocol:** | TBD |

# Protocol Synopsis

| | |
|---|---|
| **Sponsor Contact Information** | Ohio Pain Clinic<br>Amol Soin, MD<br>7076 Corporate Way<br>Dayton, OH 45458 |
| **Study Purpose** | The purpose of this study is to evaluate the effect of pulse widths <500 µsec and >1000 µsec on clinical outcomes during a temporary SCS trial. |
| **Study Design and Scope** | The proposed study is a prospective, multi-center, two-arm, randomized, crossover design to be conducted at up to 10 sites. The study will enroll up to 100 subjects in order to include up to 10 subjects in the study per site. Subjects selected to participate in the trial have back and/or leg pain, have been evaluated as a candidate for SCS and have agreed to undergo a temporary SCS trial using the Algovita® system with percutaneous leads. Each subject will be followed during the trial period of approximately 7+/-2 days.<br>The study will end when the last subject has completed the trial period and exited. The expected enrollment period for this study is approximately six months. After exit from the clinical study, subjects will continue to be followed by their physician per usual care. All device and procedure-related AEs will be collected and reported per the study protocol. |
| **Primary Effectiveness Objective** | Compare the change in the patient defined pain coverage map from baseline to the end of the 7+/-2 day trial. |
| **Secondary Effectiveness Objectives** | Secondary measures of therapy effectiveness will include:<br>• Compare the change from baseline of pain scores between the two study arms. Pain scores are obtained using the Numeric Rating Score (NRS) administered at baseline and after completion of each arm of the study.<br>• Paresthesia distribution: At end of each arm, subjects will be asked to complete a diagram that shows distribution of paresthesia.<br>• At the end of the trial period, subjects will be asked to select their favorite program.<br>• At the end of the trial period, subjects will be asked to rate the quality of the pain relief achieved during the trial (from either arm) using the following scale*; Excellent, Very Good, Good, Fair or Poor.*<br>• At the end of the trial period, subjects will be asked to rate their overall satisfaction with the pain relief achieved during the trial (from either arm) using the following scale: *Very Satisfied, Satisfied, Neither Satisfied nor Unsatisfied, Unsatisfied, or Very Unsatisfied.* |
| **Secondary Safety Objectives** | Secondary measures of therapy safety will include:<br>• Rate of device-related and/or procedure-related AEs from the Trial procedure through study completion. |

**Study Procedures**

After the subject has consented to the study, he or she will be enrolled in the clinical study and undergo a baseline evaluation. The patient will then be randomly assigned to arm one (pulse with <500 µsec) or arm two (pulse width >1000 µsec) and undergo an Algovita® trial procedures. Following the trial procedure, the subject's EPG will be set to the appropriate pulse width, based on the arm assigned, and then programmed to achieve optimal pain relief. For the next three days, the subject will evaluate pain relief generated by the 1st assigned program (arms).

After 3 days, the patient will visit the Ohio Pain Clinic for data collection and then reprogramming of the EPG for the next arm. For the next three days, the subject will evaluate the SCS therapy generated by the 2nd assigned program and then return to the clinic for data collection, removal of the leads and exit from the study. After the subject is exited from the study, he or she will be followed by the Ohio Pain Clinic per usual care. The data collection requirements are listed below.

**Enrollment:**

- Informed consent signed
- Confirmation of study eligibility

**Baseline evaluation:**

- Record pain ratings and pain map
- Relevant medical history
- Physical examination
- Brief Pain Inventory
- Demographics

**After the lead implantation:**

- Implant procedure
- Document SCS products & lead configuration, electrode position and programmed parameters

**4 and 7 day (+/– 2) Post-Implantation:**

- Record pain map data
- Record pain rating for current arm
- Record paresthesia and pain map for current arm
- Document AEs
- Program subject with next arm parameters and document

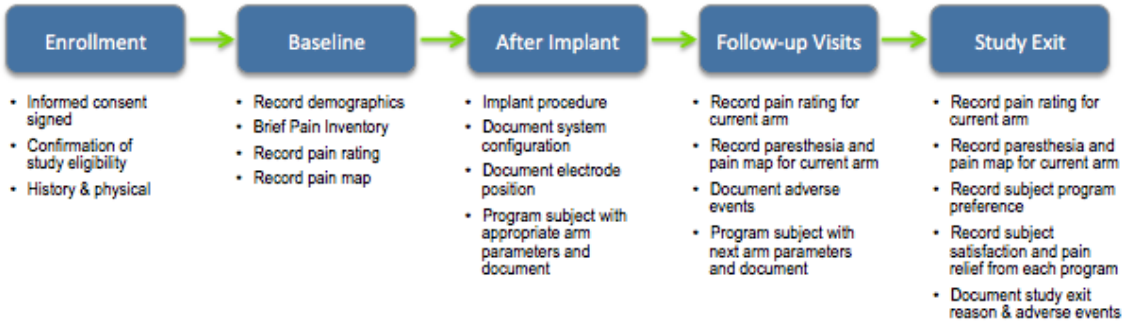
**Study Exit**

- Record pain map data
- Record pain rating for current arm
- Record paresthesia and pain map for current arm
- Record program preference
- Record satisfaction and pain relief from each program
- Document study exit reason & AEs

## TIME AND EVENTS SCHEDULE

| Assessments and Data Collection | Enrollment | Baseline | After Implant | Follow-up Visits | Study Exit |
|---|---|---|---|---|---|
| • Eligibility confirmation | ✓ | | | | |
| • Medical history<br>• Physical exam | ✓ | | | | |
| • Informed consent | ✓ | | | | |
| • Record demographics<br>• Brief Pain Inventory<br>• Record pain map | | ✓<br>✓<br>✓ | | | |
| • Implant and system information | | | ✓ | | |
| • Record paresthesia and pain map for current arm<br>• Record pain rating for current arm<br>• Document any AEs | <br>✓<br>✓ | <br>✓<br>✓ | ✓<br>✓<br>✓ | ✓<br>✓<br>✓ | ✓<br>✓<br>✓ |
| • Record subject program preference<br>• Record subject satisfaction and pain relief from each program<br>• Document study exit reason & any AEs | | | | | ✓<br>✓<br>✓ |

## FLOWCHART




## PROTOCOL HISTORY OF CHANGE

TBD Original issue

# Table of Contents

**Page**

# List of Abbreviations and Definitions

| Abbreviation/Term | Definition |
|---|---|
| ADE: | Adverse Device Event |
| AE: | Adverse Event |
| CIP: | Clinical Investigational Plan |
| CRF: | Case Report Form |
| CTA: | Clinical Trial Agreement |
| FDA: | Food and Drug Administration |
| GCP: | Good Clinical Practices |
| ICF: | Informed Consent Form |
| ICH: | International Conference on Harmonization |
| IRB: | Institutional Review Board |
| ISO: | International Organization for Standardization |
| NRS: | Numeric Rating Scale |
| PW: | Pulse Width |
| SADE: | Serious Adverse Device Effect |
| SCS: | Spinal Cord Stimulation |
| SOC: | Standard of Care |
| UADE: | Unanticipated Adverse Device Effect |
| USADE: | Unanticipated Serious Adverse Device Effect |
| µsec: | Micro Second |
| VAS: | Visual Analog Scale |

# 1.0 INTRODUCTION

Patients with chronic intractable pain of the trunk and/or limbs are typically treated on a continuum with less invasive therapies prescribed first. Established, non-surgical treatment options include, but are not limited to, oral medications, physical therapy, TENS, acupuncture, nerve blocks, radiofrequency ablation and other options based on clinical judgment. The surgical treatment options for these patients include surgery of the spine, sympathectomy, intrathecal drug pumps, and spinal cord stimulation (SCS) systems[i].

An advantage of a SCS system is that it is a reversible and nondestructive treatment option. The main principle of SCS therapy is pain suppression via the delivery of electrical signals to the spinal cord and related nerves through electrodes in the epidural space. An implantable pulse generator (IPG) is implanted under the skin, typically in the abdomen or buttock area, to generate mild electrical signals. The electrical signals typically produce paresthesia overlapping the area of pain for the patient. The IPG is programmed to deliver the electrical signals in a therapeutic manner and is then activated by the patient as needed to assist in management of their pain. SCS therapy treatment is deemed successful if there is a 50% reduction in pain as measured by a numeric rating scale or visual analog scale. The most common use of SCS therapy is for failed back surgery syndrome (FBSS) that affects up to 40% of patients who undergo spinal surgeries[ii iii iv v].

A candidate for SCS therapy is first tested by undergoing a trial procedure in which a temporary lead is implanted in the epidural space and then externalized and connected to eternal pulse generator (EPG). A temporary trial typically last 5 to 10 days and will allow the patient and doctor to determine the effectiveness of the therapy before undergoing a permanent implant.

SCS therapy has been in use since the early 1970s and has been implanted in over 600,000 patients to treat chronic pain. Over the past 30 years, SCS system technology has advanced from single channel IPGs with single contact leads to multi- channel IPGs with over 32 channels, rechargeable batteries, and lead designs improved for reliability and stability. Though the principles of operation of the SCS system have essentially remained the same, these advances have increased safety, efficacy and longevity of the therapy.

The Algovita® SCS System is similar in design and performance to newer SCS systems from other medical device companies. The FDA approved Algovita® system has many advanced features including the ability to better control the shape of the electrical pulse. One such feature is a longer pulse width range than the other systems on the market. Pulse width determines how long an electrical pulse is activated. A longer pulse width is not associated with any safety concerns as determined by the FDA. The intent and justification for this study is to understand if a longer pulse width provides better outcomes to patients.

Although the effects of pulse width are mentioned in many SCS investigations, it has been the primary focus of very few studies. Several decades ago, research was conducted into the technical aspects of SCS, including PW. In a study of SCS, Jobling showed that different patients required widely varying amplitudes of stimulation and concluded that 200 µsec was the optimum pulse duration, because it was the most energy- efficient[vi]. In 1980, Davis and Gray concurred that 200 µsec was the preferred PW to deliver adequate amplitude while conserving energy[vii]. Some published reports suggested that there was therapeutic value to having higher parameter ranges than were available on previous primary cell IPGs. In addition, longer PWs have been anecdotally described as achieving better pain-paresthesia overlap and comfort for the patient, thus potentially more effective at relieving pain[viii].

The introduction and widespread adoption of rechargeable IPGs for SCS has diminished the importance of energy efficient programming to prolong time between revision surgeries and resulted in longer pulse width settings in these systems. Gould and Bradley reported in a retrospective analysis of patient-preferred programs that over 50% of the programs used PWs in excess of 450 μs[ix]. Yearwood et al. showed that 10/19 patients had greater coverage, and 8/19 patients displayed "caudal shift" of paresthesia coverage with increased PW[x]. A mathematical model of electrical field and neural activation in SCS has shown good agreement with clinical data that a longer PW is associated with increased paresthesia coverage and a shift of the paresthesia coverage caudally[xi].

Investigation into the clinical and technical effects of PWs may be important in the continued effort to more fully understand the mechanisms of SCS. In other neurostimulation applications, varied PW has been shown to provide large and small fiber neural selectivity, where shorter PWs maximized the difference between large and small fiber thresholds[xii]. With advances in SCS technology, particularly rechargeable IPGs, patients are now being offered a wider range of parameters to treat their pain. In particular, PW programming ranges of the Algovita® system can be programmed up to 1500 μsec).

# 2.0 OBJECTIVES

## 2.1 Primary Objective

To evaluate the effect of conventional pulse widths <500 µsec and pulse widths >1000 µsec on clinical outcomes during temporary trial as measured by patient defined pain maps.

## 2.2 Secondary Objectives

Secondary measures of therapy effectiveness will include:

1. To evaluate the effect of conventional pulse widths <500µsecand pulse widths >1000µsecon clinical outcomes during temporary trial as measured by the percent reduction in targeted pain compared to baseline using the NRS at the end of the trial period.
2. At end of each arm, subjects will be asked to complete a diagram that shows distribution of paresthesia.
3. At the end of the trial period, subjects will be asked to select their favorite program.
4. At the end of the trial period, subjects will be asked to rate the quality of the pain relief achieved during the trial (from either arm) using the following scale*; Excellent, Very Good, Good, Fair or Poor*
5. At the end of the trial period, subjects will be asked to rate their overall satisfaction with the pain relief achieved during the trial (from either arm) using the following scale; *Very Satisfied, Satisfied, Neither Satisfied nor Unsatisfied, Unsatisfied or Very Unsatisfied*
6. Number of patients who achieved ≥ 50% pain relief during the trial (from either arm)
7. Rate of device-related and/or procedure-related AEs from SCS implant through study completion or study exit.

# 3.0 DEVICE

## 3.1 ALGOVITA® SPINAL CORD STIMULATION SYSTEM

This Clinical Study will include commercially released system components from the Algovita® SCS System manufactured by Nuvectra® Corporation (Plano, Texas). The materials, dimensions, method of construction, indications for use, and principles of operation of the Algovita® SCS system components are the same or functionally similar to the FDA-approved and CE marked products distributed by Medtronic, Abbott (St. Jude), and Boston Scientific.

The Algovita® SCS system is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome, intractable low back pain and leg pain.

The devices used for this study will be sourced through normal commercial channels from Nuvectra® and will not be supplied by the Sponsor.

## 3.2 REGULATORY CLASSIFICATION

The Algovita® SCS System received CE Mark in Europe on 14 June 2014 and FDA (PMA) approval in the US on 20 November 2015.

The sponsor has determined that this qualifies as a post-market study. The SCS system is being used per labeling indications and data collection have been aligned with typical data collection for SCS systems.

# 4.0 STUDY DESIGN

The proposed study is a prospective, single-center, two arm, randomized, crossover design to be conducted at The Ohio Pain Clinic. The study will enroll up to 100 subjects in order to assure at least 50 subjects in the study. Subjects selected to participate in the trial have back and/or leg pain, have been identified as a candidate for SCS and have agreed to undergo a temporary SCS trial using the Algovita® system with percutaneous leads. Each subject will be followed during the trial period of approximately 7 days.

The study will end when the last subject has completed the trial period or is exited. The expected enrollment period for this study is approximately three months. After exit from the clinical study, subjects will continue to be followed by their physician per usual care. All device and procedure-related AEs will be collected and reported per the study protocol.

## 4.1 OVERVIEW OF DATA COLLECTION AT STUDY VISITS

| Assessments and Data Collection | Enrollment | Baseline | After Implant | Follow-up Visits | Study Exit |
|---|---|---|---|---|---|
| • Eligibility confirmation | ✓ | | | | |
| • Medical history<br>• Physical exam | ✓ | | | | |
| • Informed consent | ✓ | | | | |
| • Record demographics<br>• Brief Pain Inventory<br>• Record pain map | | ✓<br>✓<br>✓ | | | |
| • Implant and system information | | | ✓ | | |
| • Record paresthesia and pain map for current arm<br>• Record pain rating for current arm<br>• Document any AEs | <br>✓<br>✓ | <br>✓<br>✓ | ✓<br>✓<br>✓ | ✓<br>✓<br>✓ | ✓<br>✓<br>✓ |
| • Record subject program preference<br>• Record subject satisfaction and pain relief from each program<br>• Document study exit reason & any AEs | | | | | ✓<br>✓<br>✓ |

Figure 4.1 Study Flowchart

# 5.0 ENDPOINTS

The endpoints of the study are focused on collecting data to determine clinical outcomes of Pulse Widths >1000µseccompared to Pulse Widths <500µsecduring an SCS trial. Safety data will also be collected at all visits. Data will be collected using:

- Patient generated Pain Maps
- The NRS to assess pain levels
- Questionnaires to assess pain coverage, program preference, overall satisfaction of the trial and AEs

## 5.1 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is defined as the percent reduction from baseline in targeted patient generated pain map coverage between the two arms.

## 5.2 SECONDARY ENDPOINTS

Endpoints for secondary measures of therapy effectiveness:

- To evaluate the effect of conventional pulse widths and pulse widths >1000µsecon clinical outcomes during temporary trial as measured by the percent reduction in targeted pain compared to baseline using the NRS at the end of the trial period.
- Comparison of paresthesia overlap of pain between each arm as evaluated by the reviewer to determine which arm had superior pain overlap (coverage)
- Patient *preference* for pulse widths >1000µsecor <500 µS
- Patient *satisfaction* for pulse widths >1000µsecor <500 µS
- Number of patients who achieved ≥ 50% pain relief during the trial (from either arm)
- Rate of device-related and/or procedure-related AEs from Trial Lead implant through study completion.

# 6.0 MINIMIZATION OF BIAS

Potential sources of bias in this study may result from selection of subjects, treatment of subjects, and evaluation of study data. The following methods have been incorporated into the study to minimize potential bias.

- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment
- Subject demographics will be collected at baseline on possible differences that may affect the primary objective
- All study clinicians, participating site personnel, and the Sponsor's personnel will be trained on their respective aspects of the study using standardized training materials
- All study clinicians will be trained on and required to follow the CIP

# 7.0 INVESTIGATORS

## 7.1INVESTIGATOR SELECTION AND RESPONSIBILITIES

In order for the Investigators to participate in the study, they must meet the following criteria:

- Curriculum vitae (CV) providing evidence of sufficient training and experience in the management of patients with chronic pain.
- Has implanted and managed at least 12 patients with SCS devices within the past 12 months.
- The Investigator's participation in other clinical studies will not present a conflict of interest and will not interfere with the clinical study enrollment, study management, or study confidentiality.
- Is willing to provide any conflicts of interest details.
- Is willing to comply with all federal laws and regulations as well as IRB rules regarding clinical studies.

# 8.0 STUDY POPULATION

Subjects that are candidates for SCS, agreed to undergo an SCS temporary trial and that meet study eligibility criteria will be asked to participate in the study and will be required to sign informed consent prior to any study-related procedures or data collection occurring. It is expected that up to 15 subjects may be enrolled to screen for eligibility, and up to 10 subjects will undergo an SCS trial with the Algovita® Trial System. Subjects may either be male or female and must meet all eligibility criteria noted below which are typical eligibility criteria for SCS system post-market studies.

## 8.1 Inclusion Criteria

To be eligible for this study, patients ***MUST***:

1. be eligible for SCS therapy according to the Algovita® SCS system Indications for Use statement
2. be undergoing a SCS trial using Algovita® SCS system
3. sign a valid, Institutional Review Board (IRB)-approved informed consent form.
4. be 18 years of age or older when written informed consent is obtained

## 8.2 Exclusion Criteria

To be eligible for enrollment in this study, the patients must ***NOT***:

1. be contraindicated for an Algovita® SCS system
2. have a cognitive impairment or exhibits any characteristic, that would limit the study candidate's ability to assess pain relief or complete study assessments
3. have a life expectancy of less than 2 years
4. be participating in another clinical study that would confound data analysis
5. have a coexisting pain condition that might confound pain ratings
6. have a significant psychiatric disorder

## 8.3 Sample Size

The study sample size is limited to 100 subjects.

# 9.0 Methods and Procedure

## 9.1 DATA COLLECTION REQUIREMENTS

Subject data will be collected and documented on case report forms (CRFs). Drafts of the CRFs for this study are located in Appendix 17.

### 9.1.1 Subject Screening Procedure

Subjects will be screened from candidates for SCS, that have agreed to undergo an SCS temporary trial and that meet study eligibility. Subjects who meet these criteria will be asked to participate in the study and if they agree will be required to sign an informed consent prior to any study-related procedures or data collection occurring.

| Assessments and Data Collection | Enrollment | Baseline | After Implant | Follow-up Visits | Study Exit |
|---|---|---|---|---|---|
| • Eligibility | ✓ | | | | |
| • Medical history<br>• Physical exam | ✓ | | | | |
| • Informed consent | ✓ | | | | |
| • Record demographics<br>• Brief Pain Inventory<br>• Record pain map | | ✓<br>✓<br>✓ | | ✓ | ✓ |
| • Implant and system information | | | ✓ | | |
| • Record pain rating for current arm<br>• Record paresthesia and pain map for current arm<br>• Document any AEs | | | ✓ | ✓ | ✓ |
| • Record subject program preference<br>• Record subject satisfaction and pain relief from each program<br>• Document study exit reason & any | | | | | ✓<br>✓<br>✓ |

Table 6-1: Summary of assessments at each visit

### 9.1.2 Informed Consent

Informed consent is defined as legally effective, documented confirmation of a subject's (or their legally authorized representative or guardian) voluntary agreement to participate in a particular clinical

investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. When a subject signs and dates the informed consent form, he/she is considered a subject enrolled in the study.

Prior to initiation of any study-specific procedures, subjects (or their legally authorized representative or guardian) must sign and date the informed consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization, or equivalent, where required by law and IRB. Documentation that consent was obtained prior to any study-related procedures must be maintained in the subject's case history.

### 9.1.3 BASELINE VISIT

Confirm subject's eligibility for study participation and perform a Baseline visit. The following data will be collected by the study physician during this assessment and documented as appropriate:

- Relevant medical history (including diagnosis, prior treatment for chronic pain, past surgical procedures)
- Demographics
- Physical examination
- Collection of Brief Pain Inventory, pain-related ratings (NRS) and pain map

### 9.1.4 IMPLANT

The implant trial procedure will be performed within 28 calendar days following the Baseline Visit. Appropriately trained field staff will assist as necessary with the Algovita® Trial Lead implant. The recommended placement for the device will be determined by the physician and documented on the CRF. Information regarding the devices used, location, and procedure data will be collected on an Implant CRF. A Nuvectra® representative may be present during the implant procedure and may assist in the programming of the Algovita® system at the Investigator's direction.

### 9.1.5 FOLLOW-UP VISITS

Follow-up visits will occur at day 4 and 7 (+/–2) post-implantation. Data collected at these visits will be recorded on case forms (CRFs) and will include:

- Record paresthesia and pain map for current arm
- Record pain rating for current arm
- Document AEs
- Program subject with next arm parameters and document

### 9.1.6 STUDY EXIT

A Study Exit CRF must be completed for any subject who signed an informed consent form, as they are considered enrolled in the study. Data to be collected at this visit includes:

- Record paresthesia and pain map for current arm
- Record pain rating for current arm
- Record program preference

- Record satisfaction and pain relief from each program
- Study exit date and reason for study exit

Additional data that will be collected as they occur include:

- Device or procedure related AEs
- Technical Observations/Device Deficiencies
- Surgical Interventions

The following scenarios may lead to study exit and will require completion of a Study Exit CRF.

- Inclusion/exclusion criteria not met
- Subject ineligibility for implant, in the opinion of the study physician
- SCS lead removal without re-implantation
- Implant attempted, however no SCS was implanted
- Voluntary withdrawal by subject
- Investigator chooses to withdraw a subject
- Failure to maintain adequate study compliance
- Subject Death

# 10.0 ADVERSE EVENT REPORTING

## 10.1 ADVERSE EVENTS

At each evaluation, the investigator will determine whether any adverse events (AE's) have occurred. For the purpose of this protocol, an adverse event is any undesirable clinical occurrence in a subject that can be attributed to the device or incision closure procedure.

In this study, patients should be encouraged to report AE's spontaneously or in response to general, non-directed questioning (e.g., "How has your health been since the last visit?"). Any time during the study, the patient may volunteer information that resembles an AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF.

The following categories of adverse event severity are to be used:

| | |
|---|---|
| **Mild** | Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae |
| **Moderate** | Interferes with the patient's usual activity |
| **Severe** | Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes events that cause fetal distress, fetal death, congenital abnormality or malignancy or any permanently disabling event. |

## 10.2 ANTICIPATED ADVERSE DEVICE EFFECTS

The following ANTICIPATED EVENTS have been identified as possible complications of implanting neurostimulator leads.

- Infection at implant site
- Pain at implant site
- Bleeding
- Bruising
- Device failure
    - Unintended stimulation
    - Increased stimulation
    - Decreased stimulation
    - Lead breakage/migration
    - Battery depletion
    - Erosion of device
    - General device failure

## 10.3 UNANTICIPATED ADVERSE DEVICE EFFECTS

Unanticipated adverse device effects are 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 the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

For the purposes of this study, serious is defined as any significant adverse experience, including those which may be either life-threatening or involve permanent or long term injuries, but excluding injuries that are non-life-threatening and that are temporary and reasonably reversible.

**An Investigator must submit to the sponsor and to the responsible Medical Ethics Committee ( IRB ) any unanticipated adverse device effects occurring during the study as soon as possible, but in no event later than ten (10) working days after the Investigator first learns of the effect.**

Contact Name:

Erin Dewenter, RN
Ohio Pain Clinic
7076 Corporate Way
Dayton, OH 45458

| Report | Submit To | Description/Constraints |
|---|---|---|
| Death | Sponsor | Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event. |
| | IRB | Submit to IRB per local reporting requirements. |
| Unanticipated adverse device effect (UADE)[1] | Sponsor | Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event. |
| | IRB | Submit as soon as possible but no later than 10 working days after the Investigator first learns of the event, or per local reporting requirements, whichever is more conservative. |
| Other Adverse Device Effects | Sponsor | Submit or report as required per local reporting requirements. |
| | IRB | Submit or report as required per local IRB reporting requirements. |
| | Regulatory Body | Submit or report as required per regulations. |

Table 11-1: Investigator adverse event reports

# 11.0 STATISTICS

## 11.1 Study Population

All patients who received treatment will be included in an intent-to-treat (ITT) analysis. A per protocol analysis will also be conducted if there are protocol violators.

## 11.2 Safety Analysis

All patients who received treatment will be included in the safety analysis. The proportion of patients with complications will be compared by Fisher's Exact test. The two treatment groups will be compared using t-test for continuous variables and chi square test for category variables. All adverse events will be listed and the frequencies, severity, and relationship to the treatment procedure will be tabulated and compared by treatment groups.

# 12.0 ETHICS

## 12.1 Medical Ethics Committee ( IRB ) Review

Prior to initiation of the study, the Principal Investigator will submit the study protocol, sample Informed Consent Form, and any other documents that may be requested, to the IRB for review and approval. The Principal Investigator and will request that the IRB provide written approval of the study and will keep on file all IRB correspondence including records of approval of all documents pertaining to this study. If the IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), the Sponsor will prepare the required documents and send them to the Investigator for reporting to the IRB.

## 12.2 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, good clinical practices (GCP), and the applicable regulatory requirements.

## 12.3 Patient Information and Consent

Prior to screening for the study, each patient, as required, will be informed in detail about the nature of the clinical investigation with its expected risks and discomforts. The basic elements of informed consent as specified by the EU Directive 2001/20/EC will be followed. Written consent will be obtained from each patient as required, to be involved in the clinical study by using the IRB -approved Informed Consent Form. The Principal Investigator will verify the consent form. Each patient will be given a copy of the Informed Consent Form. The patients will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Prior to the start of the study, the Principal Investigator will provide with an actual Informed Consent Form approved by the IRB for use during the study. At the conclusion of the study, the Principal Investigator will provide a letter to stating that a signed informed consent was obtained from each of the study patients. The signed informed consent forms will be kept on file at the study site for the required period of time.

# 13.0 STUDY ADMINISTRATION

## 13.1 Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the Principal Investigator and study site. Compliance will be confirmed by the study monitor during the pre-study visit. The pre-investigational requirements may include:

1. Current Curricula Vitae and current medical licenses or medical numbers of the Principal Investigator and all sub-investigators
2. IRB name and address; Department of Health and Human Services (DHHS) number, if applicable, or membership list
3. Written documentation of IRB approval of protocol (identified by protocol number and title) and informed consent document (identified by protocol number and title)
4. A copy of the IRB approved consent form (that has also been approved by )
5. A signed Clinical Research Agreement
   - Provisions for direct access to source/data documents if necessary for study-related monitoring, audits, IRB review, and regulatory inspection.

## 13.2 Clinical Supplies

The Principal Investigator will be responsible for the dispensing, inventory, and accountability of all clinical supplies, exercising accepted medical practices. An accurate and timely record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection by the Clinical Monitor and upon request. Upon completion or termination of the study the Principal Investigator will return all remaining clinical supplies to , or designee along with a copy of the inventory record and a record of the clinical supplies returned. Under no circumstances will the Principal Investigator allow the investigational device to be used other than as directed by this protocol.

## 13.3 Case Report Forms (CRFs)

will provide the CRFs. The Principal Investigator will be responsible for the timeliness, completeness, and accuracy of the information on the CRF. All entries must be legibly recorded in ink, with entry errors designated by a single-line cross out, initialed and dated, such that the original entry remains readable

The Principal Investigator will make these forms available for review and collection by the designated representative at each scheduled monitoring visit.

The Principal Investigator will retain a file copy of each completed CRF. In addition, the Principal Investigator will ensure that the monitor representative(s) have access to source

documents (e.g., hospital and clinic records) to ensure accuracy and completeness of the CRFs during the periodic reviews.

## 13.4 Study Completion

Data and materials that are required before the study can be considered complete and/or terminated are:

- Laboratory findings, clinical data, and all special test results from treatment through the end of the follow-up period
- CRFs (including correction forms) properly completed by appropriate study personnel and signed by the Principal Investigator
- Completed Device Accountability Records
- Statement of outcome for each unanticipated adverse device effect reported
- Copies of protocol amendments and IRB approvals (if applicable)

## 13.5 Final Report

The purpose of this single center pilot study is to assess the clinical performance of Wireless stimulator device when used to treat UUI. The results will be presented in a clinical report presented by with the study data provided by the Primary Investigator (PI).

## 13.6 Retention of Study Records

The Principal Investigator will retain copies of the approved protocol, completed CRFs, informed consent documents, relevant source documents, study-related correspondence and all other supporting documentation related to the project for the latter of a period of 2 years following the approval of a premarket application (U.S.) or 2 years from the time the study is terminated.

These files must be made available for inspection upon reasonable request by authorized representatives of the Ohio Pain Clinic.

## 13.7 Confidentiality

Patient medical information obtained by the study is confidential and disclosure to third parties other than those noted below is prohibited.

At the patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of Nuvectra, and the IRB s (if appropriate).

The information obtained in this study may be published in medical journals, but will not reveal the identity of the individual patients.

## 13.8 Publication of Study Results

Results of this study will not be submitted for presentation or publication without the prior written permission of .

# 14.0 SIGNATURE of PRINCIPAL INVESTIGATOR

I have read the study protocol, entitled Single center pilot study to show efficacy of a neurostimulator for the treatment of refractive UUI. I agree to conduct the investigation in accordance with the agreement, the investigational plan and applicable EU and US regulations. Further, I agree to conduct the investigation in accordance with the conditions imposed by the reviewing IRB /IRB. This includes the supervision of the device involving human patients and ensuring that the requirements for obtaining informed consent are met.

Principal Investigator Date

# 15.0 Declaration of Helsinki

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**
**Ethical Principles for Medical Research Involving Human Subjects**

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

1. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

2. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed participants in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

## 3. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

# 16.0 REFERENCES BIBLIOGRAPHY

[i] American Chronic Pain Association Resource Guide to Chronic Pain Medication and Treatment, 2014 Edition.

[ii] North RB. Failed back surgery syndrome: 5-year follow-up in 102 patients undergoing repeated operation. *Neurosurgery,* vol. 28, p. 685–90, 1991.

[iii] Wilkinson HA. The Failed Back Surgery Syndrome: Etiology and Therapy, 2nd edition., Philadelphia: Harper & Row, 1991.

[iv] Law JD. Reoperation after lumbar intervertebral disc surgery. *J Neurosurg,* vol. 48, p. 259–63, 1978.

[v] Lehmann TR. Repeat lumbar surgery: A review of patients with failure from previous lumbar surgery treated by spinal canal exploration and lumbar spinal fusion. *Spine ,* vol. 6, p. 615–9, 1981.

[vi] Jobling DT, Tallis RC, Sedgwick EM, Illis LS. Electronic aspects of spinal-cord stimulation in multiple sclerosis. Med Biol Eng Comput 1980; 18:48-56

[vii] Davis R, Gray E. Technical factors important to dorsal column stimulation. Appl Neurophysiol 1981; 44:160-170.

[viii] Meyerson B. Commentary on: Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: Analysis of technical drawbacks and solutions. Neurosurgery 1997; 40:990-999.

[ix] Gould B, Bradley K. Pulse width programming in spinal cord stimulators. Abstract of the American Academy of Pain Medicine 22nd Annual Meeting, 2006 February 22-25. San Diego, CA

[x] Yearwood TL, MD, Hershey B, Bradley K, Lee D. Pulse Width Programming in Spinal Cord Stimulation: A Clinical Study. Pain Physician 2010; 13:321-335

[xi] Lee D, Hershey B, Bradley K, Yearwood T. Predicted effects of pulse width programming in spinal cord stimulation: a mathematical modeling study. Med Biol Eng Comput (2011) 49:765–774

[xii] Grill WM, Mortimer JT. The effect of stimulus pulse duration on selectivity of neural stimulation. IEEE Trans Biomed Eng 1996; 43:161 – 166.