Investigational Device Exemption Protocol for Intrathoracic Nerve Stimulation

NCT04066374

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Table of Contents

Protocol Synopsis

Study Title	Intrathoracic Nerve Stimulation
Investigational Devices	Medtronic Intellis, Spinal Cord Stimulation (SCS)
Sponsor-Investigator	Usman Ahmad, M. D. Assistant Professor of Surgery, CCLCM of CWRU Director, Thoracic Robotic Surgery Program Department of Thoracic & Cardiovascular Surgery Cleveland Clinic 9500 Euclid Ave, J4-1, Cleveland, OH 44195 216 444-1921 AHMADU@ccf.org
Study Purpose	The purpose of this study is to conduct an early clinical evaluation of SCS, which will provide initial insight into the clinical safety and function of the device to determine if peripheral nerve stimulation (PNS) of the intercostal nerves using an electrical lead placed in the thoracic cavity is a safe and effective method of pain control after cardiothoracic surgery.
Study Design	Prospective, single-center, non-blinded, non-randomized IDE study of the SCS for pain control after cardiothoracic surgery.
Primary Endpoints	a. Pain as measured by the visual analog scale b. Freedom from bleeding, infection, pneumothorax, arrhythmias
Secondary Endpoints	a. Morphine equivalents taken (both IV and PO) during the inpatient period b. Number of narcotics taken post discharge c. Pain control as measured by the McGill pain questionnaire.
Patient Population	Inclusion criteria: • Patients undergoing pulmonary surgery by open thoracotomy or thoracoscopy with or without robotic assistance. Exclusion criteria: • Woman who is pregnant, • Subjects who have an active systemic infection or are immunocompromised, • Subjects who will be exposed to diathermy or MRI,

	• Subjects who have an electrically active implant, e.g., cardiac pacemaker, defibrillator, or neurostimulator, • Subjects who are on anticoagulation therapy that would preclude their ability to undergo the implant procedure, • Subjects less than 22 years of age, • Subjects at elevated risk of infection or bleeding, • Subjects unable to consent on their own, • Subjects with active infection, • Subjects with immunocompromised state, • Subjects with preoperative chest pain, • Subjects with pleural space infection or inflammatory process, • Subjects undergoing esophageal, tracheal, or gastric procedures, • Subjects undergoing pneumonectomy, • Subjects with an uncorrectable coagulopathy, • Subjects who are allergic or have shown hypersensitivity to any materials of the neurostimulation system which come in contact with the body.
Number of Subjects	10
Number of Sites	1
Sample Size Justification	The sample size is 10 subjects. No formal sample size calculations were performed, as this study is not hypothesis driven.
Study Hypothesis	This is not a hypothesis driven study. Descriptive summary statistics will be presented.
Duration of Study	Expected enrollment period is 6 months, follow-up duration is up to 3 months (screening, procedure, POD 0 to discharge, and a follow-up visits or phone call by POD 14, 1 month and 3 months. Total duration of the study is 1 year.
Study Monitor	Medical monitor will review all AEs. Site monitoring will be performed internally by Cleveland Clinic Clinical Research Personnel.

Purpose

The purpose of this study is to conduct an early clinical evaluation of Spinal Cord Stimulation (SCS), which will provide initial insight into the clinical safety and function of the device to determine if peripheral nerve stimulation (PNS) of the intercostal nerves using an electrical lead placed in the thoracic cavity is a safe and effective method of pain control after cardiothoracic surgery.

Background

Despite minimally invasive techniques in thoracic surgery, postoperative pain can still be an issue for patients. Achieving adequate pain control not only affects a patient's short and long term quality of life but is also extremely important in preventing post-operative complications. Pain hinders with ambulating earlier and in performing pulmonary toilet hence increasing the risk of ensuing complications. While surgeons use multimodal approaches (e.g., epidural, regional anesthesia, NSAIDs, and opioids) to treat the postoperative pain, patients may not find relief in the acute period. Additionally, the use of opioids in the postoperative period can lead to chronic dependence and misuse. According to the Center for Disease Control, nearly 25% of patients chronically dependent on opioids started taking narcotics after they underwent a surgical procedure. Every day more than 115 people a day die from narcotics, and costing the United States $78.5 billion dollars a year. To prevent the need for opioids and their associated side effects, we look beyond medications for postoperative pain control.

The field of neuromodulation has been studying the effects of magnetic field and electrical current stimulation of different areas of the body to treat pain. While this has been shown to be effective for complex regional pain syndrome, low back pain, migraines and post herpetic neuralgia, there have not been studies applying the same concept to patients in the acute postoperative period. Our goal is to apply the same concept of peripheral nerve stimulation to treat post thoracic surgery pain and decrease the need for opioids for pain relief.

The purpose of this IDE is to study the efficacy of peripheral nerve stimulation in treating post thoracic surgery pain and the safety of using these stimulation leads in the thoracic cavity.

Report of Prior Investigations

The Medtronic Intellis device is currently FDA approved for long term spinal cord stimulation to treat chronic low back pain (**PMA# P840001/S344**). The goal of our IDE study is to show the efficacy and safety of this device in an off-label use for peripheral nerve stimulation within the thoracic cavity. Specifically, we want to determine if using the Medtronic Intellis device in the thoracic cavity to stimulate the intercostal nerves is a safe and effective method of pain control in the acute post thoracic surgery period.

Electrical Intercostal Nerve Stimulation

Subcutaneous Electrical Intercostal Nerve Stimulation

Listed below are two case reports detailing the use of electrical nerve stimulation directly over intercostal nerves, using subcutaneously tunneled electrical leads. Two patients with chronic thoracotomy pain underwent trials of medication and transcutaneous electrical nerve stimulation (TENS) without success[1]. After eight and ten-day trials of peripheral nerve stimulation (PNS) where significant pain control was reported for both patients (Visual Analog Scale 0/10 pain), both patients then underwent permanent St Jude's Octrode and Quattrode lead

placement in the subcutaneous space over the area of pain[1]. Both patients reported significant improvement in quality of life and no longer required narcotics or antiepileptics for chronic pain[1].
The second case report involved a 13-year-old boy with chronic epigastric abdominal pain after undergoing a right nephrectomy for a malrotated right kidney. He underwent subcutaneous placement of the St. Jude permanent Octrode stimulator over the right lower intercostal nerves corresponding with D11[2]. The patient noted significant acute pain control and within four months, he no longer required Fentanyl patches for pain control[2]. Ten months after placement, the patient was off all narcotic pain medications as well as gabapentin[2].

Both case reports did not mention any adverse events[1-2]. Listed below are the stimulators used and the associated device settings.

Study	Manufacturer	Stimulator	Leads Accepted per Device	Effective Current (mA)	Effective Pulse Width (microsec)	Effective Frequency (Hz)	Lead	Condition
Tamimi et al (2009) Neuromodulation[1]	St. Jude (was Advanced Neuromodulation Systems)	Eon IPG	2	2-3	140-150	25-30	St. Jude percutaneous leads 4 or 8 contacts 8 contact span 52 mm Quattrode/Octrode	Chronic post thoracotomy pain
Johnson (2010) Ann R Coll Surg Engl[2]	St. Jude (was Advanced Neuromodulation Systems)	Eon IPG	2	2-3	500	80	St. Jude percutaneous lead 8 contact 60 mm span PN 3186	Chronic intercostal upper abdominal pain

Transcutaneous Electrical Nerve Stimulation (TENS) of Intercostal Nerves

TENS applies the same principles as electrical stimulation, but rather than placing a device directly over the nerves, TENS can be placed over the skin. Multiple randomized control trials have been conducted comparing TENS to other methods of pain control in the immediate post-operative period for thoracic surgery[3-5].
In a double blinded randomized placebo control trial, patients undergoing posterolateral thoracotomy were treated with TENS (n=60) or placebo (n=56) for five days following thoracic surgery[3]. Primary outcome was patient reported pain control as measured by the visual analog scale (VAS)[3]. Secondary outcomes were pulmonary function as measured by forced expiratory volume in one second (FEV1), forced vital capacity (FVC), partial arterial oxygen pressure (PaO_2), partial arterial carbon dioxide pressure ($PaCO_2$)[3]. Additionally, the amount of pain medications administered were also compared[3]. At every time point, TENS was associated with superior pain control at rest and when coughing. This translated into a decreased amount of opioids taken by the TENS group compared to the control group[3]. Additionally, this translated to superior pulmonary function in the TENS group compared to the placebo control group[3]. There were no side effects in the TENS group, whereas the placebo control group had more nausea, vomiting and pruritus related to increased opioid use[3]. This same study was

replicated in another double blinded RCT involving fifty thoracic surgery patients in Italy. In addition to patient reported pain levels, opioid consumption and pulmonary function, the investigators also tracked inflammatory marker serum levels[4]. This trial also found that TENS was associated with improved patient reported pain (VAS), improved pulmonary function (FEV1), and decreased opioid use in the TENS group compared to the placebo group. The investigators also found that TENS was associated with lower serum levels of inflammatory markers IL-6, IL-10, and TNF-α[4]. It is unlikely that the lower serum levels of inflammatory markers is related to any difference in surgeries between the two groups, as both groups were well balanced in the procedures performed. The lower serum levels of cytokines in the TENS group was attributed in part to the TENS application[4]. However, the mechanism is not well understood.
In a randomized trial comparing TENS (n=20) to paravertebral block (PVB, n=20), both were effective in treating post thoracic surgery pain[5]. The authors found that patients who received PVB experienced less pain both at rest and while coughing, which translated to less opioid use[5]. While there are concerns that PVB would cause hypotension, hemodynamic parameters did not differ among groups; however, FEV1/FVC was higher in the TENS group compared to the PVB group indicating superior recovery of pulmonary function in the TENS group[5]. TENS is able to provide some pain relief, however because of added subcutaneous tissue layers between the stimulation device and the peripheral nerves, the effects are not as magnified as peripheral nerve stimulation using implantable leads.

Medtronic Intellis, Spinal Cord Stimulation (SCS)

Long term implantable spinal cord stimulation devices have been well validated in treating chronic pain conditions including complex regional pain syndrome, low back pain, migraines and post herpetic neuralgia[6-14]. This technology was first developed in 1967 and FDA approved in 1989[14]. SCS and PNS both employ alternating currents at specific frequencies to generate magnetic fields that stimulate nerves to provide pain relief. Exact mechanisms are not well understood, however likely involve gate theory[13]. Common complications of implantable SCS and PNS include infection (3.6 – 17.9%)[15], bleeding, lead migration (9-25%)[14-15], lack of efficacy (21%)[15], or mechanical failures (3.6%)[15] that may include failed connections in leads, and breakage of leads. The rates of these complications vary based on placement location, the duration of use, and the method of placement (e.g. ultrasound, fluoroscopic). Medtronic announced the FDA approval of their Intellis device September 18, 2017, which was designed to be smaller and overcome battery life and MRI compatibility limitations of other devices[14]. This device is currently being used by pain specialists and neurosurgeons to treat chronic low back pain.

Off Label Use and Preliminary Data

While this device is currently designed for long term placement in the body, our goal is to repurpose the technology for an acute period of time after thoracic surgery. After IRB approval (IRB 18-434 Intrathoracic Peripheral Nerve Stimulation Placement) we performed a pilot study showing that a similar flat paddle lead (St. Jude Lamitrode88) can be placed and removed safely intraoperatively without bleeding complications or injury to surrounding structures. Five patients underwent thoracic surgery under video thoracoscopic guidance. At the conclusion of the case as chest tubes were placed, we placed a paddle lead along the posterior chest wall perpendicular to the intercostal nerves under direct visualization. The leads were secured at two fixed points, one at the skin incision using a suture (the same manner as securing chest tubes), and the other fixed point under a short pleural bridge within the thoracic cavity. This fixation technique is designed to mitigate the risk of lead migration. Additionally, because this device will only be employed for as long as the chest tubes are in the chest (range 3-7 days), there should be lower risk of infection and bleeding/erosion compared to permanent SCS or PNS.

Alternative Therapies

Current alternative therapies include systemic opioids, epidural, paravertebral blocks, intercostal nerve blocks, and transcutaneous electrical nerve stimulation. Despite the multitude of therapeutic options, patients still can have uncontrolled pain and discomfort. It is important to note that while analgesics instilled through an epidural catheter can provide effective pain control, the procedure is invasive, operator dependent and carries significant risks that can sometimes be prohibitive. More importantly this can only be used in a small subset of patients who do not have an infection and do not need anticoagulation. In addition, epidural catheters can only be placed in fully awake and cooperative patient in completely elective and planned settings.

Additionally, these alternatives are not without their own side effects. Beyond potentially addictive effects, opioids in the short-term cause nausea, vomiting, itching, constipation, respiratory depression, and hypotension. Epidurals and paravertebral block efficacy are user dependent on the person placing the device, which varies. Additionally, there is added operative time with both of these techniques. While TENS is helpful, its limited effectiveness has prevented widespread adoption in cardiothoracic surgery.

Study Device and Technique Description

Intraoperative

At the conclusion of the thoracic operation while the lung is still deflated, when the chest tubes are about to be placed, a 1 cm wide pleural tunnel will be created with electrocautery in one intercostal space. The flat paddle lead will be slipped through the tunnel under direct visualization perpendicular to the intercostal nerves in the paraspinous space next to where the nerves exit the spine. The Blake drain will be placed in the posterior chest lateral to the paddle lead and the chest tube will be placed anterior to the lung per usual care. The anesthesiologist will then inflate the lung and we will confirm that the leads remain in place and that the chest is hemostatic. The lead, Blake drain, and chest tubes will then be secured at the skin in the usual manner and the incisions will be closed. Figure 1A-C.

Depending on the patient's anatomy and location of incisions, 2-3 paddle leads may be needed for appropriate coverage of all intercostal spaces. All leads will be placed in the same fashion.

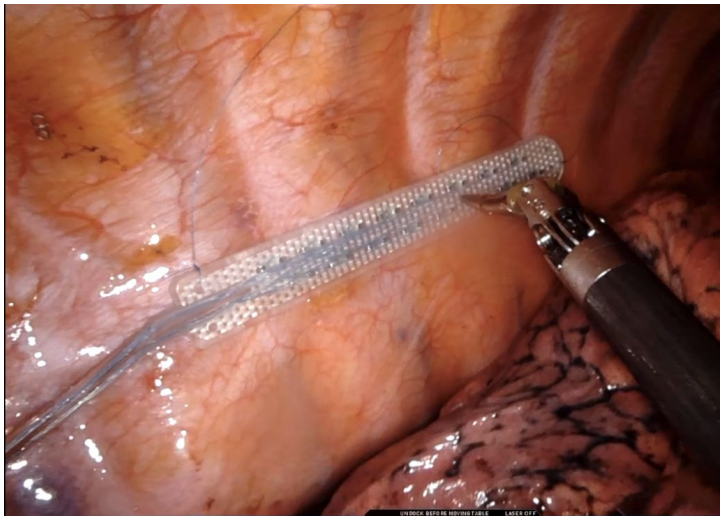


Figure 1A Flat paddle lead placed within the thoracic cavity at the conclusion of the procedure while the lung is still deflated.

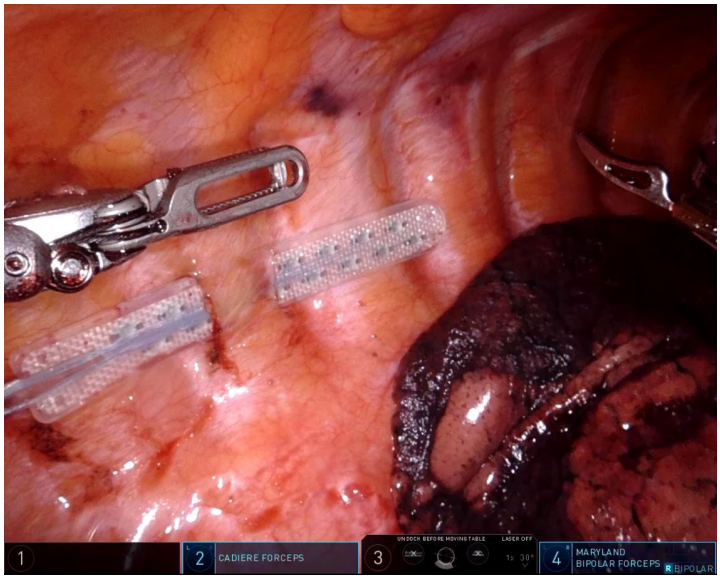


Figure 1B A second point of fixation within a pleural tunnel created intraoperatively. The other point of fixation (not shown) is at the skin level.

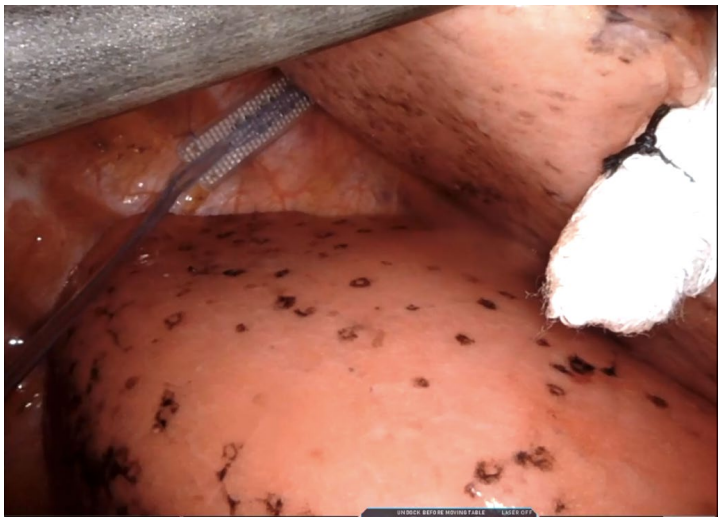


Figure 1C Flat paddle lead remains flat against the chest wall once the lung is inflated at the conclusion of the procedure.

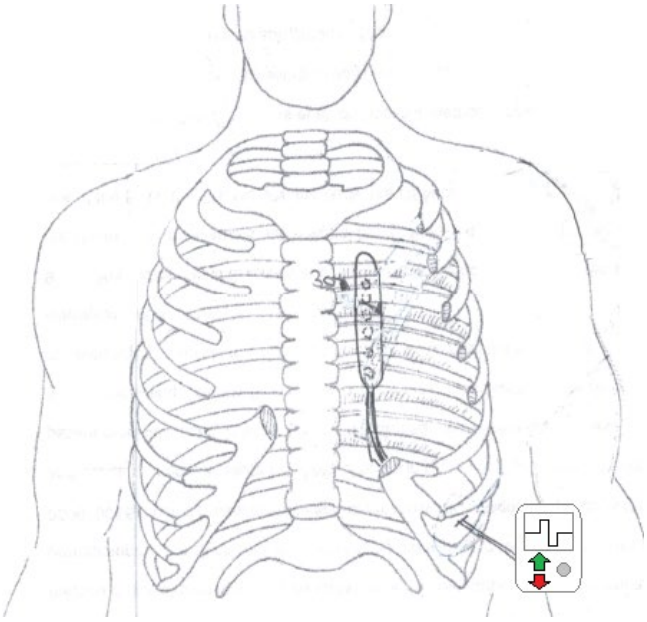


Figure 2: Internally placed paddle(s) connected to externally placed pulse generator

Postoperative

After the patient is taken from the operating room to recovery, a postoperative chest x-ray (CXR) will be obtained as part of standard clinical care. This will confirm that the paddle lead, Blake drain, and chest tubes remain in the correct orientation after patient transport to postoperative recovery. The device will be tested and programmed in the immediate postoperative period once the patient has sufficiently recovered from anesthesia. The patient will be able to toggle between different stimulation programs based on their preference for pain control during the trial. During each day of the trial, the patient will have the opportunity to have new programs added as needed. The patient will be able to arrest stimulation at any time if it causes discomfort.

Daily CXR will be obtained as part of the usual postoperative care. On CXR, it is standard routine to evaluate heart and lung fields as well as chest tube locations. Additionally, the investigators will evaluate the paddle lead location on CXR as well.

A clinical programmer will adjust the device settings as needed for patient comfort. Patient reported pain level as measured by the VAS will be recorded every four hours as per standard nursing protocol during the inpatient stay. These will be documented in the patient's chart and recorded by the research personnel.

Removal

The device must be and will be removed before the patient is discharged from the hospital. The average length of a hospital stay is 3-4 days; however, depending on the subject's condition, it may be longer than 7 days. Once it is deemed that the patient no longer requires the chest tubes, the paddle lead will be removed the same way a drain or chest tube is removed. The paddle lead will be removed before the chest tube is removed to mitigate risk of pneumothorax. The stitch securing the paddle lead to the skin will be cut and the patient will be asked to take in a deep breath and hold it. The paddle lead will then be swiftly and smoothly removed from the chest cavity and an

occlusive Vaseline gauze will be placed over the skin incision where the paddle lead had exited. A CXR after paddle lead and chest tube removal will be obtained confirming that there is no pneumothorax or hemothorax as a result of lead removal.

Rescue Medications - Fentanyl PCA 20 mcg q 10 min up to 6 doses per hour until they have reliable oral intake. Then 5-10 mg of oxycodone q 4-6 hours can be utilized per clinical guideline when subjects require rescue medications. Tylenol is given as a standard clinical protocol. Type and number of narcotics medications taken will be collected and reported.

Number of patients/sites

10 patients to be recruited at one site, the Cleveland Clinic Main Campus.

Study Duration

Expected enrollment period is 6 months, follow-up duration is up to 3 months, and total duration of the study is 1 year.

Patient Characteristics

Inclusion criteria:

- Patients undergoing pulmonary surgery by open thoracotomy or thoracoscopy with or without robotic assistance.

Exclusion criteria:

- Woman who is pregnant,
- Subjects who have an active systemic infection or are immunocompromised,
- Subjects who will be exposed to diathermy or MRI,
- Subjects who have an electrically active implant, e.g., cardiac pacemaker, defibrillator, or neurostimulator,
- Subjects who are on anticoagulation therapy that would preclude their ability to undergo the implant procedure,
- Subjects less than 22 years of age,
- Subjects at elevated risk of infection or bleeding,
- Subjects unable to consent on their own,
- Subjects with active infection,
- Subjects with immunocompromised state,
- Subjects with preoperative chest pain,
- Subjects with pleural space infection or inflammatory process,
- Subjects undergoing esophageal, tracheal, or gastric procedures,
- Subjects undergoing pneumonectomy,
- Subjects with an uncorrectable coagulopathy,
- Subjects who are allergic or have shown hypersensitivity to any materials of the neurostimulation system which come in contact with the body.

Subject Recruitment and Informed Consent Process

All patients must provide informed consent prior to any study related procedures being performed. Patients are assessed for acceptability into the study by the study investigators. If they meet the inclusion criteria, the

possibility of the utilization of pain control by the neuro-stim IDE will be discussed in hospital exam rooms or the outpatient clinic.

The investigator will review the patient's history, physical examination, and radiographic studies prior to obtaining informed consent. An IRB approved informed consent form will be obtained from the patient after the purposes of the study, the risks, expected discomforts, and potential benefits have been explained. Because of the need for emergency or urgent operations, the informed consent form may be signed by the patient or by a family member / proxy. Copies of the informed consent will be included in the study records. Another copy will be given to the patient for their records.

Primary Outcome Measures

Primary outcome:

a. Pain as measured by the visual analog scale
b. Freedom from bleeding, infection, pneumothorax, arrhythmias

Secondary Outcome Measures

Secondary outcome:

a. Morphine equivalents taken (both IV and PO) during the inpatient period
b. Number of narcotics taken post discharge
c. Pain control as measured by the McGill pain questionnaire.

Hypothesis Testing

This is not a hypothesis driven study. Descriptive summary statistics will be presented for all data points.

Data Collection and Analysis

The data will be collected in a 21CFR part 11 compliant database, REDCap Cloud. No statistical analysis beyond counts and frequencies will be required. The results of this study will be described in a case report format.

Pre-Procedure Screening:

History and physical will be performed to ensure that the subjects meet the inclusion criteria and do not meet any of the exclusion criteria of the study. Women of child-bearing potential, the pregnancy test will be performed prior to the procedure.

Subjects will be asked to answer Mc Gill Pain Questionnaire as a baseline assessment.

Inpatient Days:

Visual analog pain assessment and morphine equivalence will be collected. Daily chest X-ray will be taken and findings will be collected until discharge.

Follow-up:

Subject will return at 2 weeks, 1 month, and at 3 months for pain assessment. If subjects are unable to return, a phone visit will be performed to collect pain assessment and AE assessment.

Follow-up Schedule Table:

Procedures	Screening	Intraoperative	POD 0	POD 1 to Day of Discharge	First outpatient postoperative visit (POD 7 -14)	1 month (POD 21 – 31)	3 months (POD 45 – 90)
McGill Pain Questionnaire	X				X	X	X
Peripheral nerve stimulator placement		X					
Peripheral nerve stimulator activation			X	X			
Peripheral nerve stimulator removal				X			
Visual Analog Scale Pain assessment			X	X	X	X	X
Chest X-ray			X	X (daily until dc)			
Number of Narcotics Taken			X	X	X	X	X
Assessment of AE		X	X	X	X	X	X

Subject Withdrawal from the Study

A subject may withdraw from the study at any time and should notify the investigator in this event. The investigator may also withdraw the subject from the clinical study at any time based on his medical judgment.

Subject Lost to Follow-up

A subject will be considered lost to follow-up and terminated from the study once they have missed two consecutive appointments without contacts and three attempted contacts are unanswered (it must include a contact with certified letter).

Risk Assessment and Adverse Events

Definition of Adverse Events (AE):

An adverse event is an untoward medical occurrence or exacerbation of an existing medical condition subsequent to the experimental therapy. For this study, adverse events are rated in the following ways:

- Anticipated (anticipated, not anticipated)
- Device and procedure relationships (unrelated, possibly related, or related)

Adverse events will be categorized as either serious or non-serious. A Serious Adverse Event (SAE) is an event that meets at least one of the following:

- Is fatal
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Results in permanent impairment of a body function or permanent damage to a body structure
- Results in hospitalization or prolongs a hospitalization
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

Definition of an Unanticipated Adverse Device Effect (UADE) :

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 application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

Risks and Risk Mitigations Strategy:

The purpose of this study is to assess the safety of an electrical stimulation lead in the thoracic cavity. Summary of some of the known risks is identified below; however, there may be risks that are not known or unforeseen at this time. The severity of any particular event may vary depending on the subject's pre-existing conditions or comorbidities. AEs will be collected and classified as device-related, procedure-related or unrelated; events that are related to pre-existing condition are not considered as AEs.

Adverse events associated with the application of this procedure may include, but are not limited to, the following (the severity of any particular event may vary depending on the patient's pre-existing conditions or comorbidity):

Possible AE	Likelihood	Severity	Risk Mitigation Strategy
Discomfort	Less likely	Mild	Very little discomfort is expected. Subjects will have traditional pain

			management methods available to them as well.
Bleeding	Rare	Mild to moderate	It is unlikely that that this device will cause bleeding. If there is bleeding related to the device, then the treatment may range from watchful waiting to blood transfusion and to reoperation.
Infection	Rare	Mild to moderate	It is unlikely that this device will cause infection. If there is infection related to the device, then the device will be removed. The treatment may range from intravenous antibiotics to reoperation.
Mechanical failure of the lead (lead displacement, lead fracture, wire fracture)	Rare	Mild to moderate	It unlikely that this device will have mechanical failure. If there is lead/wire fracture then this would require reoperation. If leads are displaced then the treatment can range from watchful waiting to device removal.
Device malfunction	Rare	Mild	It is unlikely that the device will malfunction. If the device is not functional, then a new stimulator will be attached to the stimulator leads. If there is not a functional stimulator available, then the leads will be removed.
Arrhythmia	Rare	Mild to moderate	It is unlikely that there will be arrhythmias caused by the electrical leads. The patients will be attached to the cardiac monitors during the postoperative stay, as per standard care. If the patient develops an

			arrhythmia, then the stimulator will be turned off. If this resolves the arrhythmia, then it will be noted that the device likely caused the arrhythmia. If the arrhythmia persists despite the device being turned off, then it is unlikely that the device is the cause of the arrhythmia. If there is suspicion that the lead itself, even while turned off, is responsible for an arrhythmia, then the lead will be removed.
Pneumothorax	Rare	Mild to moderate	It is unlikely that a patient will have a pneumothorax after lead removal. To mitigate this risk, the lead will be removed prior to chest tube removal. Treatment may range from nonoperative management to chest tube placement.

All AEs will be captured via electronic data capture (EDC) system.

Expected Benefits

If the device works the way we expect it to, then the patient should experience pain relief and potentially some paresthesia in the distribution of the intercostal nerves affected. Effective pain control will allow the patient to mobilize earlier in the hospital stay and perform pulmonary toilet functions more effectively without the side effects of systemic opioids or epidurals.

Medical Monitor

To ensure consistent and accurate AE reporting and classification, an independent medical monitor will be established. The medical monitor will assess all AEs captured by the study coordinator(s).

Monitoring

Study monitoring will be performed by experienced and appropriately trained personnel appointed by the sponsor-investigator to ensure that the investigation is conducted accordance with the FDA IDE regulations. Monitoring will be conducted by the independent monitor in CCF HVI Research Department.

HVI (Heart and Vascular Institute) Research Department
Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland, OH 44195

On-site monitoring will occur at regular intervals throughout the duration of the trial, and monitor visit with summary of findings will be outlined in monitoring report.

Monitoring activities will include:

- Study Initiation visit
- Review of training and delegation of authority log
- Review of FDA/IRB approval letters and correspondences
- Review of informed consent to ensure:
  - That the subject signed and dated the informed consent form for him/herself
  - A valid and effective version (reviewed and approved by the IRB) of the consent form was used
  - That the informed consent process was appropriately documented
- Confirmation that the study staff is conducting the study in compliance with the protocol approved by the IRB.
- Source Document Verification (i.e., review all subjects' charts for: study eligibility, primary and secondary endpoints data, and that the protocol specific source documents are on file)
- Ensuring the data reported on the eCRF is consistent with the source documentation
- Review of outstanding queries on the eCRF
- Review of all subject research records to ensure the following:
  - All AEs and SAEs have been reported including any abnormal exam findings determined to be clinically significant;
  - AEs have been reviewed, attribution has been assigned and signed by investigator in a timely manner;
  - EAEs and SAEs have been submitted to the IRB and FDA per IRB/FDA reporting criteria; and
  - All deaths have been reported appropriately
- Ensuring any protocol deviation that meets reporting requirements has been reported to the IRB as well as reported in eCRF
- Ensuring investigational products have been properly handled
- Verification of device used
- Study termination/closure visit

IRB

The protocol shall be evaluated and approved by the Institutional Review Board at the Cleveland Clinic Foundation prior to proceeding with the study.

Institutional Review Board
Alan Lichtin, MD – IRB Chairman
Cleveland Clinic Foundation
9500 Euclid Avenue, OS 1
Cleveland, OH 44195
(216) 444-5848

Investigator Agreement

Dr. Usman Ahmad, as a study Sponsor and P.I. will certify all participating investigators will sign the investigator agreement and no investigator will be added until the investigator agreement is signed in accordance with 21 CFR 812.29(b)(5).

Investigator responsibilities include, but not limited to:

- Conducting the study in accordance with the investigational plan, signed agreement and applicable regulations protecting the rights and safety of study subjects
- Informing all subjects that the device being utilized is for investigational purposes, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met
- Ensuring that IRB approval is secured prior to staring the study and ensuring continuing review and approval as required throughout the investigation
- Ensuring and supervise all associates, colleagues, and employees assisting the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments
- Maintaining adequate and accurate records and ensuring those records are available for inspection at any time
- Ensuring that conducting the study does not give rise to conflict of interest
- Controlling of all investigational devices

Device Charges

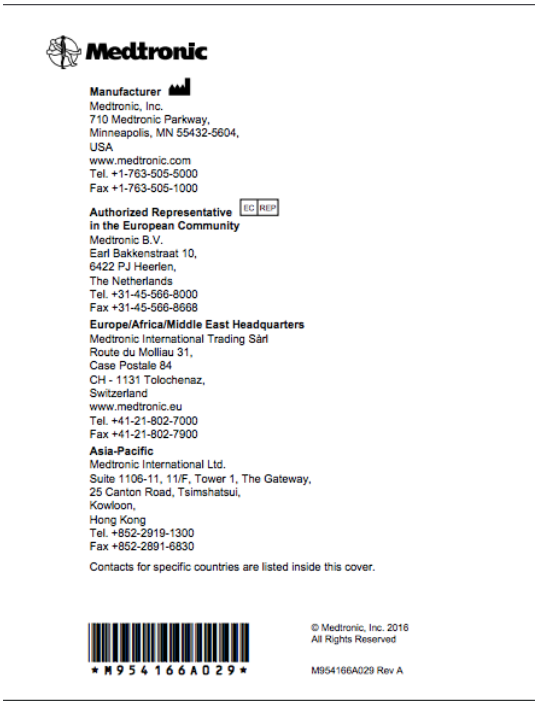
The device will be charged at the same amount charged by the manufacturers of the devices to the hospital. The devices that are used as part of their clinical care is billed to the subject and or his/her medical insurance.

Manufacturing Information

The **Medtronic Intellis Spinal Cord Stimulation (SCS)** is manufactured, sterilized and packaged by Medtronic. We will not be tampering or adjusting the packaging in any way.

Labeling

Sample Label:



Medtronic

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Reports

Deviation from the Investigational Plan: The sponsor-investigator will notify the reviewing IRB and FDA of any deviation from the investigational plan to protect the life of physical well-being of a subject in an emergency. The notice will be provided as soon as possible but no later than 5 working days after the emergency occurred. If the change or deviation may affect the scientific soundness of the investigational plan or the rights, safety or welfare of the subject, the sponsor will obtain prior IRB and FDA approval for deviation by submitting an IDE supplement.

UADE: The sponsor-investigator will report the results of an evaluation of an unanticipated adverse device effect to FDA and IRB within 10 working days after the sponsor-investigator first receives notice of the device adverse effect.

Withdrawal of IRB approval: The sponsor-investigator will notify FDA of the withdrawal of IRB approval or any part of the investigation within 5 working days of receipt of withdrawal of approval.

Progress report or annual reports: The sponsor will provide progress reports to the reviewing IRB and to the FDA. In addition, the sponsor will submit interim progress reports summarizing the outcomes will be provided after the initial 5 subjects return for their first post-operative follow-up visit to the IRB and FDA.

Recall and device dispositions: The sponsor-investigator will notify FDA and reviewing IRB of any request that a sponsor-investigator return, repair, or dispose of any unit of an investigational device. The notice will be made within 30 days after the request is made and will state why the request was made.

Final report: The sponsor-investigator will notify FDA and reviewing IRB within 30 working days of the completion or termination of the study. The sponsor-investigator will also submit a final report to FDA and reviewing IRB within 6 months after the completion or termination of the study.

Failure to obtain informed consent: The sponsor-investigator will submit a report of the use of a device without first obtaining informed consent. The report will be made to the FDA within 5 working days after receipt of notice of such use.

Other reports: The sponsor-investigator will provide accurate, complete, and current information about any aspect of the investigation upon request from the reviewing IRB or FDA

References

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2. Johnson, Rd, Al Green, and Tz Aziz. "Implantation of an Intercostal Nerve Stimulator for Chronic Abdominal Pain." *The Annals of The Royal College of Surgeons of England*92, no. 3 (2010). doi:10.1308/147870810x12659688851474.
3. Erdogan, Mükerrem, Abdullah Erdogan, Nazmiye Erbil, Hanife (Kabukcu) Karakaya, and Abid Demircan. "Prospective, Randomized, Placebo-controlled Study of the Effect of TENS on Postthoracotomy Pain and Pulmonary Function." *World Journal of Surgery*29, no. 12 (2005): 1563-570. doi:10.1007/s00268-005-7934-6.
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9. Kemler MA., De Vet HCW., Barendse GAM et al., The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. Ann Neurol; 55: 13-18 (2004).
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13. Peterson, Erika A., and Konstantin V. Slavin. "Peripheral Nerve/Field Stimulation for Chronic Pain." In *Neurosurgery Clinics of North America*, 789-97. Vol. 25. 2014.
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