Clinical Study Protocol
Amendment-1

A single-center, randomized, pilot study to assess iovera° lumbar medial branch cryoneurolysis vs lumbar radiofrequency ablation for facet mediated chronic low back pain

Protocol No.:	CRS-107
Original Protocol Date:	11APR2022
Amendment-1 Date:	06FEB2023
Study Device:	iovera®°
Principal Investigator:	[redacted]
Sponsor:	The Albany & Saratoga Centers For Pain Management [redacted] [redacted]

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

Title of Study: A single-center, randomized, pilot study to assess iovera° lumbar medial branch cryoneurolysis vs lumbar radiofrequency ablation for facet mediated chronic low back pain

Principal Investigator(s): [redacted]

Study Center(s): One center in the United States (US)

Publications (Reference): None

Objectives:

Primary objective: The primary objective of this study is to assess the safety and feasibility of iovera° lumbar medial branch cryoneurolysis vs. radiofrequency ablation (RFA) for facet mediated chronic low back pain (CLBP).

Secondary objectives: The secondary objectives of this study are to:

1. Evaluate safety outcomes (i.e., adverse device effects, serious adverse device effects, adverse events [AEs]) related to iovera° treatment vs. RFA;
2. Evaluate clinical outcomes related to iovera° vs. RFA treatment including pain, functional disability, and concomitant medication use (including opioids and analgesics);
3. Evaluate the treatment success and failure rate of iovera° medial branch cryoneurolysis vs. RFA;
4. Evaluate subject satisfaction with pain management;
5. Identify subgroups of patients who are most and least likely to benefit from iovera° medial branch cryoneurolysis for facet mediated CLBP.

Methodology:

This is a single-center, randomized, pilot study in adult subjects with facet mediated CLBP. Thirty (30) subjects are planned for initial enrollment and will be randomized 1:1 to receive iovera° medial branch cryoneurolysis or radiofrequency ablation.

This study is designed to determine if a full efficacy RCT can be successfully conducted using the procedures and protocols described in the current pilot study protocol, or if protocol modifications are necessary before moving forward with a full efficacy RCT. Furthermore, the study will assess the feasibility of the outcome measurements employed, construct a foundation for sample size calculation, and the acceptability/practicality of conducting the full efficacy RCT.

Randomization to treatment groups according to the randomization assignment will be performed on the day of treatment. The treatment groups are:

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

- **Group 1:** subjects will receive iovera° cryoneurolysis to the medial branch nerves of the lumbar spine
- **Group 2:** subjects will receive RFA to the medial branch nerves of the lumbar spine

Screening

Subjects will be screened within 30 days of the scheduled iovera° medial branch cryoneurolysis or RFA procedure to determine their eligibility. Subjects must provide informed consent – as documented in a study informed consent form (ICF) before performing any study related procedure that differs from the standard of care (SOC) at the study site.

During the screening visit, subjects will be assessed for past or present neurologic and general medical conditions that in the judgment of the Investigator would preclude them from study participation. No procedures other than the site's SOC will be performed before signed informed consent is obtained. After the ICF is signed, demographic information, medical and surgical history, concomitant medications/concurrent procedures information, and vital signs will be collected. Assessment of the intended treatment areas will be conducted. Subjects will assess their pain in the low back region using the Numeric Rating Scale (NRS). Subjects must be instructed to report any adverse device effects and adverse events (AEs) to the Investigator from the time the ICF is signed through Day 360 (±7 days).

When screening test results are received and the subject is deemed eligible for the study, the subject will be notified that he or she is enrolled in the study.

Method of Assigning Subjects to Treatment

Randomization scheme

This is a randomized pilot study. The study will enroll 30 total subjects 1:1 to receive iovera° medial branch cryoneurolysis or radiofrequency ablation on the day of treatment.

The randomization code will be computer generated.

Randomization Procedures

Once a subject is identified as being qualified for the study in accordance with the eligibility criteria, the Investigator or designee will obtain a randomization assignment on the day of treatment. The subject will be considered randomized into the study once the study treatment is assigned.

Replacement of Subjects

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

Subjects who withdraw from the study before the study treatment procedure may be replaced. Once a subject number is assigned, subject numbers will not be reused; subjects enrolled to replace those who withdraw will be assigned a unique subject number and randomized to treatment according to the procedures outlined above.

Subjects who are randomized but are withdrawn from the study before receiving the study treatment procedure may be replaced. Additionally, subjects may be replaced if insufficient and/or incomplete data are noted on safety or clinical outcomes.

Diagnostic Medial Branch Block (MBB)

As part of the eligibility criteria, subjects must have undergone two successful diagnostic medial branch blocks consisting of two positive blocks with local anesthetic only (i.e., no steroids) under fluoroscopic guidance that results in at least 50% relief of primary (index) pain for the duration of the local anesthetic used.

iovera° Medial Branch Block

iovera° Treatment

The iovera° system consists of a reusable, portable Handpiece, along with single patient use sterile Smart Tips (i.e., cryoprobes) and disposable nitrous oxide (N_2O) cartridges. The iovera° system produces the desired effect through initiation of a cooling cycle. Each cooling cycle is initiated by fully inserting the Smart Tip into the selected procedure site and activating the cryogen flow. The Smart Tip needles are made of stainless steel and have a closed tip, fully enclosing the cryogen. The "190" Smart Tip will be used in this study.

Administration Technique

iovera° is to be administered in the lumbar spine at the target medial branch nerves encompassing one level above and below the involved vertebral levels.

Subjects will receive a fluoroscopic guided iovera° medial branch block. Blocks will be performed with the subject in the prone position under asepsis in the following manner:

- Record start time of procedure
- The investigator injects 1% Lidocaine at the treatment site to numb the skin and tissue around the facet joint
- The iovera° Smart Tip is positioned appropriately and a fluoroscopic image is taken to confirm the Tip's position
- The iovera° Smart Tip is inserted through the skin wheal to the target medial branch nerve below the junction of the superior articular and transverse process

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted] **Name of Device:** iovera° System		

- Using intermittent fluoroscopic screening with oblique views, the Smart Tip is advanced until it strikes bone as close as possible to the target nerve
- The iovera Smart Tip is positioned, and an x-ray image is taken to confirm the Smart Tip's position
- With the desired Smart Tip position confirmed, the iovera° handpiece is secured to the Smart Tip. The start/stop button on the iovera° handpiece is then pressed to start the cycle.
- After the cycle is complete, the Smart Tip can be removed, and the next treatment cycle can commence, ensuring an overlap of the ice ball (if necessary)
- The Smart Tip is removed and bandages are applied as needed
- Record stop time of procedure and number of nerves treated

One freeze cycle will be applied to fully treat the nerve above and below the target joint. The exact process will be repeated on the opposite side of the same vertebral level, and the total time to place the probe should be recorded. For example, if one level is affected, four nerves will be treated (i.e., two nerves bilaterally), and if two levels are involved, twelve nerves will be treated (i.e., six nerves bilaterally).

Note: the subject may be offered midazolam 2-4 mg IV for sedation prior to the procedure.

A complete step-by step administration guide will be provided for the study.

Radiofrequency Ablation

The RFA system consists of a Cosman, G4 Generator. The needles used are 20-gauge, 10cm long with a 10mm active tip manufactured by Cosman. A grounding pad, also manufactured by Cosman, is placed on the upper thigh for each procedure and connected to the G4 Generator.

Radiofrequency Ablation Procedure

Radiofrequency ablation is to be administered in the lumbar spine at the target medial branch nerves encompassing one level above and below the involved vertebral levels.

Subjects will receive a fluoroscopic guided RFA medial branch block. Blocks will be performed with the subject in the prone position under asepsis in the following manner:

- Record start time of procedure
- The Right L4, L5, S1 articular pillars are identified with fluoroscopy at each level and the target points are located

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted] **Name of Device:** iovera° System		

- A skin wheal is formed using a mixture of 5mL of 1% Lidocaine and 5mL of 0.25% Bupivacaine over the target site subcutaneously and deeply
- A 20-gauge, 10cm needle with a 10mm active tip is inserted using a 15-degree oblique view and a 15-degree caudad angle onto the waist of each pillar at each level under fluoroscopic guidance
- Anterior-posterior and oblique neuroforamen views confirm positioning to be outside of the neuroforamen and in correct position at each level
- Stimulation is performed and recorded to confirm proper needle placement by the Cosman G4 RF Unit at 50 Hz up to 1.5 volts with no stimulation of the sensory or motor roots noted at each level
- Impedance is within appropriate limits at each level
- A mixture of 3mL of 0.25% Bupivacaine, 2mL of 1% Lidocaine and 1mL of 40mg/mL Triamcinolone is divided and injected at each level
- A lesion is then performed at each level at 80 degrees centigrade for 60 seconds (all lesions are at 80 degrees for 60 seconds)
- The investigator should confirm that no blood is aspirated, no cerebrospinal fluid is aspirated, and there are no paresthesias
- The needles are removed, and bandages applied to the puncture sites
- The same procedure is carried out on the opposite side
- Record stop time of procedure and number of nerves treated
- Radiographs are saved

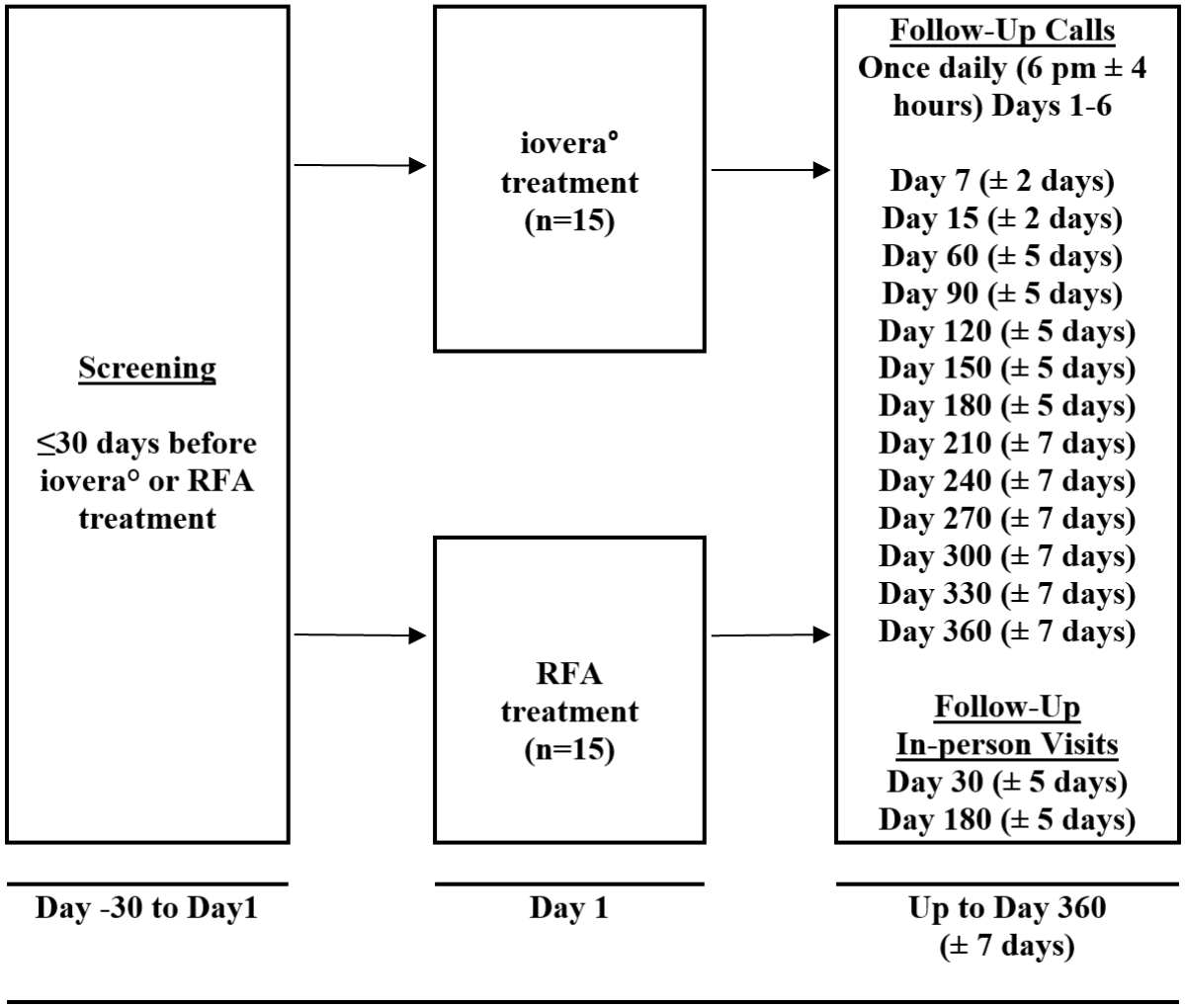
Note: the subject may be offered midazolam 2-4 mg IV for sedation prior to the procedure.

A complete step-by step administration guide will be provided for the study.

Study Schema:

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

Figure 1 Study Schema



Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

Clinical Assessments

Study assessments are presented in Table 1, Table 2, and below in the sections describing, Health Outcomes Assessments, and Safety Assessments.

Post iovera° or RFA treatment, subjects will report their pain scores (using the NRS pain scales to assess pain in the low back region) through Day 360 (±7 days).

At the Day 30 follow up visit, the subject may undergo additional clinical assessments, at which point, it may be determined that the subject will need to under other interventional procedures (including injections). For the purposes of this study, the subject may only undergo major joint and bursa injections, and injections to other regions of the spine not part of the lumbosacral spine (i.e., the subject will not be allowed to have injections in the lumbar spine and sacrum).

Number of Subjects (Planned):

A total of 30 subjects are planned for this pilot study.

Eligibility Criteria:

Inclusion Criteria:

Subjects must meet all of the following inclusion criteria to be eligible for participation:

1. Male or female volunteers, at least 18 years of age at screening
2. Primary complaint of axial low-back pain suggestive of unilateral or bilateral facet joint involvement (i.e., facet mediated CLBP)
3. Low back pain is chronic (i.e., > 3 months' duration)
4. Low back pain score of ≥ 4 (i.e., moderate pain) on the 0 to 10 NRS or functional impairment at screening
5. Successful trial of two diagnostic medial branch blocks consisting of two positive blocks with local anesthetic only (i.e., no steroids) that results in at least 50% relief of primary (index) pain for the duration of the local anesthetic used or history of a positive response to prior radiofrequency treatment (i.e., ≥ 6 months prior to enrollment)
6. Failure of at least three months of conservative non-operative therapy (e.g., physical therapy, chiropractic care, spinal injections, NSAIDs or other appropriate analgesics),
7. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria will not be eligible for participation in this study:

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted] **Name of Device:** iovera° System		

1. Active workers' compensation, personal injury, Social Security disability insurance (SSDI), or other litigation/compensation related to the spine
2. Serious spinal disorders (verified on magnetic resonance imaging (MRI)) that may impact outcomes, including any of the following:
   a. Suspected cauda equina syndrome (e.g., bowel/bladder dysfunction)
   b. Infection
   c. Tumor
   d. Traumatic fracture
   e. Systemic inflammatory spondyloarthropathy
   f. Lumbar radiculopathy/radiculitis (i.e., root irritation and deficit)
   g. Neurogenic claudication
3. Prior lumbar spinal fusion surgery
4. Comorbidity that, in the judgment of the Investigator, may affect the subject's ability to participate in the study including lumbar radiculopathy and neuropathic pain disorder
5. Currently pregnant, nursing, or planning to become pregnant during the study
6. Known contraindication to study devices, including any of the following:
   a. Cryoglobulinemia
   b. Paroxysmal cold hemoglobinuria
   c. Cold urticaria
   d. Raynaud's disease
   e. Open and/or infected wounds at or near the treatment site
   f. Coagulopathy
7. 3.5-inch needle cannot be used in the low back region because of habitus
8. Severe chronic pain disorder that in the opinion of the investigator may impact postsurgical outcomes
9. Presence of any of the following:
   a. Spinal neurostimulator
   b. Intrathecal analgesic drug pump
10. Current manifestation of poorly controlled mental illness that in the opinion of the investigator may meaningfully impact treatment outcomes, including any of the following:
    a. Mood disorder (e.g., major depression, bipolar)
    b. Psychotic disorder (e.g., schizophrenia)
11. Subject received other spine intervention/therapies in the 30 days prior to block administration (e.g., spinal injections, minimally invasive therapies, surgical therapies)
12. Subject received radiofrequency ablation in the low back region ≤ 6 months before study enrollment
13. History, suspicion, or clinical manifestation of:

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted]		
Name of Device: iovera° System		

a. Alcohol abuse or dependence
b. Illicit drug use
c. Opioid abuse or dependence (≥40 mg MED PO/day in past 30 days)

Given the COVID-19 pandemic, the subject must be medically fit/cleared for treatment by the investigator. If there is a concern about a subject's recent or potential exposure to COVID-19, or if the subject is not medically fit/cleared for treatment due to suspected COVID-19 illness/symptoms (or other serious illness), the subject must be excluded per *Exclusion criterion #4*.

Study Device:

Name: iovera° System

Duration of Subject Participation in Study:

Participation will begin at the signing of the study ICF. No more than 30 days should pass between signing of the ICF and the iovera° or RFA treatment procedure. Subjects will be followed up for 360 days (± 7 days) after iovera° or RFA treatment. Therefore, subjects may participate in the study for up to 392 days.

Study Stopping Rules

The study may be terminated if the Investigator, or officials from regulatory authorities identify conditions during the study that indicate so.

The Investigator will review all serious adverse device effects and serious adverse events (SAEs) reported from the clinical study on an ongoing basis and in real time (i.e., as the events are reported). The Investigator will be responsible for temporarily halting the study if the type, frequency, or seriousness/severity of such events suggests a potential threat to the safety of the study participants. If such action is taken, a thorough review of all available data will be conducted. Based on the results of this review and discussions with the Investigator and/or regulatory authorities as warranted, the study may be restarted or permanently terminated.

[redacted]

- [redacted]
- [redacted]

In addition, any death will be thoroughly reviewed, and appropriate action taken.

Removal of Subjects from Therapy or Assessment

Every reasonable effort will be made to maintain subject compliance and participation in the study. Reasons for discontinuation of any subject from the study will be recorded.

If any clinically significant event or condition is uncovered during the study period that might render the subject medically unstable or compromise the subject's post-treatment course, the subject will be withdrawn from the study and the event or condition will be reported as an AE or SAE.

If a subject withdraws from the study and has an ongoing AE, every effort will be made to follow up on such events until satisfactory resolution is obtained or further follow-up is otherwise no longer warranted.

Withdrawal Secondary to Adverse Events

If a subject, experiences an AE that renders the subject incapable of continuing with the remaining assessments, the subject will be discontinued from further participation in the study. A final evaluation, including the early termination assessments will be performed so that the subject's study participation can be terminated in a safe and orderly manner.

Any subject who discontinues because of an AE will be instructed to notify the study personnel of any abnormal symptoms and to visit the study site if medical evaluation is needed and the urgency of the situation permits. Any subject exhibiting AEs will receive appropriate treatment at the discretion of the Investigator until resolution of the AE.

This study involves a single treatment (i.e., iovera° or RFA); therefore, subjects will not be terminated from the ongoing study assessments as long as they are willing and able to continue with the follow-up schedule according to the protocol. For emergencies and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the Investigator and appropriate information captured in the subject's case report form (CRF). After termination from the study, the subject may be followed for safety including monitoring of AEs through Day 360.

Voluntary or Study Investigator Withdrawal

Subjects are free to discontinue from the study at any time, without prejudice to future treatment. A subject may be discontinued from the study if the subject refuses study treatment or refuses to comply with study procedures. Subjects will be encouraged to complete the study safety assessments. Reasons for discontinuation from the study will be recorded.

Early Termination Assessments

In case of early termination, the following assessments shall be performed:

- Record date, time, and reason of withdrawal
- Review adverse events; any ongoing AEs/SAEs will need to be followed to resolution

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted] **Name of Device:** iovera° System		

- Record responses to pain assessment:
  - Pain intensity scores on the NRS as "How much pain are you experiencing in your low back **right now**?"
  - Pain intensity scores on the NRS as "What was your **worst** pain in the past 24 hours in your low back?"
  - Pain intensity scores on the NRS as "What was your **average** pain in the past 24 hours in your low back?"

Clinical Assessments:

The following measurements will be assessed at the times specified:

- Pain intensity scores in the low back region using an NRS measured as follows:
  - Current pain intensity (i.e., pain "right now" in the low back region) in the low back region at Screening, day of iovera° or RFA treatment (pretreatment), once daily (at 6 pm ±4 hours) from prior to iovera° or RFA treatment to Days 1-6, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).
  - Daily pain intensity (i.e., average / worst pain over the past 24 hours in the low back region) at Screening, once daily (at 6 pm ± 4 hours) from Days 1-6 after iovera° treatment, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).
- Concomitant medication use (including opioids and analgesics) at Screening, from Days 1-6 after iovera° or RFA treatment, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).
- Functional disability at Screening, Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).
- Patient global impression of change at Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted]		
Name of Device: iovera° System		

- Patient satisfaction with pain management at Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).

[redacted]

Feasibility Endpoints:

The results of this pilot study will show if the study as designed is feasible. One of the following outcomes will be adopted at the conclusion of the trial:

[redacted]

Health Outcomes Assessments:

Health outcome assessments will include:

- Subject satisfaction with pain management
- Oswestry Disability Index (ODI)
- Patient Global Impression of Change (PGIC)

Safety Assessments:

Adverse device effects, serious adverse device effects, AEs (including neurologic adverse events), and SAEs will be recorded from the time the study ICF is signed through Day 360 (± 7 days). Any concomitant medications used to treat AEs through Day 360 (± 7 days) will also be recorded.

Any other adverse events reported during the study follow-up will also be assessed as safety outcomes.

The concepts of AEs and SAEs represent regulatory instruments used to evaluate and monitor the safety of clinical study subjects. Therefore, these terms only apply in light of their regulatory definition. The term serious, in a regulatory sense, does not necessarily mean

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

severe. The SAE concept is used primarily to identify, during the conduct of the study, those SAEs that may require expedited reporting to regulatory authorities.

Definitions

Adverse Device Effect: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) associated with the use of a device in subjects, whether or not considered related to the device. This also includes adverse device effects related to the use of a device resulting from failure, insufficient or inadequate instructions for use, improper or inadequate design, deployment, implantation, installation, or operation, or any malfunction of the device, as well as any event resulting from user error (or use error) or from intentional misuse of the device.

Medical Device Report (MDR) Reportable Event: A report of a death, serious injury, or malfunction which reasonably suggests that the device:

- May have caused or contributed to a death or serious injury, or
- Malfunctioned and the malfunction of the device would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. It is presumed that once a malfunction has occurred, it will recur.

Serious adverse device effect: An adverse device effect which results in any of the consequences characteristic of a serious adverse event:

- Results in death
- Is immediately life-threatening (i.e., an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more severe)
- Results in permanent impairment of a body function or permanent damage to a body structure; or
- Requires in-patient or prolonged hospitalization
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- Results in fetal distress, fetal death, or is a congenital anomaly or birth defect

"Permanent" means irreversible impairment or damage to a body structure or function, excluding impairment or damage that is reversible. A life-threatening injury meets the definition of serious injury, regardless of whether the threat was temporary.

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

Malfunction: Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

Unanticipated Adverse Device Effect: Any serious adverse effect on health or safety, 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, application (including a supplementary plan or application), or approved labeling, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse Drug Event Definitions

Adverse Event (AE): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE can be any unfavorable and unintended change in a body structure or body function. Adverse events include any clinically significant deterioration of a subject's medical status. The AE may involve any organ or system and can be represented by the new onset or deterioration of a disease, a syndrome, a symptom, a physical sign, as well as by findings and results of instrumental examinations and laboratory tests. Any medically relevant and untoward change after the subject signs the ICF, including frequency or pattern changes for a fluctuating condition (e.g., migraine) is considered an AE.

Serious Adverse Event (SAE): An untoward medical occurrence with a drug that at any dose:

- Results in death
- Is immediately life-threatening (i.e., an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically may have caused death, if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

- Is an important medical event where medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate, such as events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in above definition. Examples of such events include intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

Unexpected Adverse Event: An adverse event in which the nature, severity, or frequency of the event is not consistent with the safety information described in the Reference Safety Information of the Investigator Brochure or approved product labeling.

Collection and Assessment of Adverse Device Events and Adverse Drug Events

All adverse events (adverse device events, serious adverse device events, device malfunctions, AEs, SAEs) will be collected from the signing of the ICF until Day 360 (± 7 days), regardless of whether or not they are considered related to the study device, surgical treatment, and/or drugs used as part of the treatment regimen. For the study device, malfunctions will also be collected.

Any medical condition noted before the subject signs the ICF will be recorded as Medical History and is considered a pre-existing condition. Planned hospitalization for a pre-existing condition or a procedure described in the protocol, without a deterioration of health, is not considered a serious adverse device event or SAE. If a pre-existing condition changes (i.e., becomes more severe or more frequent) at any time after the ICF is signed, or after study treatment, it is considered an adverse device event and/or AE.

Investigators are not obligated to actively seek safety information after conclusion of the study participation. However, if the Investigator learns of any serious adverse device event or SAE, including a death, after Day 360 (or at any time after the subject has been discharged from the study), and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the appropriate regulatory body.

Severity of Adverse Device Effects and Adverse Drug Events

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

The severity (or intensity) of an adverse device event or AE should be categorized using the following guidelines:

- Mild: An adverse device event or AE that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An adverse device event or AE that is discomforting and interferes with normal everyday activities.
- Severe: An adverse device event or AE that prevents normal everyday activities.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

<u>Relationship of Adverse Device Effects to Study Device and Adverse Events to Drugs</u>

The Investigator is required to assess the relationship of the adverse device event, malfunction, and/or AE to study device and/or medication received for each occurrence after careful medical consideration on a case-by-case basis. The determination of the causal relationship to the study device and/or drug(s) will be made using the definitions below:

- Unrelated: A causal relationship can be easily ruled out (e.g., based on the temporal sequence, absence of a reasonable pathophysiological mechanism, or direct evidence of actual cause).
- Unlikely: A clinical event with a temporal relationship to study device and/or drug(s) administration which makes a causal relationship improbable and in which other drugs, chemicals, or underlying disease provide a plausible explanation;
- Possible: A clinical event with a reasonable time sequence to administration of the study device and/or drug(s) but which could also be explained by a concurrent disease or other drugs or chemicals;
- Probable: A clinical event with a reasonable time sequence to administration of the study device and/or drug(s) unlikely to be attributed to a concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on withdrawal (dechallenge); or
- Definite: For the study device, it is clear that it caused or contributed to the adverse device event and there is no indication of other causes. For drug(s), the pharmacological properties of the study drug(s) or of the substance class, and the course of the AE after dechallenge and, if applicable, after rechallenge, and/or

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

specific test indicate involvement of the study drug(s) in the occurrence/worsening of the AE, and no indication of other causes exists.

An additional causality assessment is required for malfunction reports.

Likely to Cause or Contribute to a serious adverse device event	For device malfunctions that have not already been associated with a serious adverse device event, there is a reasonable possibility that death or serious injury may occur if the malfunction were to recur.

Outcome of Adverse Events

The Investigator will assess the outcome of the adverse device event and/or AE after careful medical consideration, on a case-by-case basis. General guidelines are provided below:

Recovered/Resolved:	The event resolved and the subject recovered from the AE.
Recovered/Resolved with Sequelae:	The initial event resolved but has a continuing abnormal condition as a result of the AE.
Not Recovered/ Not Resolved:	At the time of last assessment, the event was ongoing, with an undetermined outcome. Note: ongoing AEs are not to be considered resolved as a result of death
Recovering/Resolving:	At the time of last assessment, the event was decreasing in frequency, severity, etc., and a resolution was expected.
Fatal:	The AE directly caused death.
Unknown:	There was an inability to access the subject or the subject's records to determine the outcome (e.g., subject withdrew consent or was lost to follow-up).

Action Taken with Subject due to an Adverse Device Effect or Adverse Drug Event

The Investigator will provide any actions taken regarding the subject (e.g., treatment, diagnostic tests, laboratory tests, or therapy) for each reported adverse device event and AE.

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

- None.
- Medication.
- Non-pharmaceutical therapy (the specific therapy used must be recorded in the CRF).
- Discontinued from study.
- Other (the specific action taken must be recorded).

Reporting of Serious Adverse Device Events and SAEs

All serious adverse device events, malfunctions, and SAEs will be captured in the subject's case report form within 24 hours of the site becoming aware of the event. Serious adverse device event/SAE or malfunction forms will be reported in accordance with local regulations.

The serious adverse device event /SAE report will provide as much of the required information as is available at the time. The following minimum information is required for reporting a serious adverse device event /SAE: subject identifier, reporting source, event, causality assessment, and event outcome.

During the time period between treatment and study discharge, subjects will be instructed to contact a designated member of the research team if they experience any adverse device effects or AEs during this period. The Investigator and qualified designees will enter the information in the electronic data capture (EDC) system as instructed.

Follow-up of Serious Adverse Device Events and SAEs

Investigators will not wait to receive additional information to fully document the event before notifying the appropriate body of the serious adverse device event, malfunction, or SAE. The initial report should be followed by a full written summary in the EDC detailing relevant aspects of the SAE in question. Where applicable, the investigator will report any information relevant to the serious adverse device event malfunction, or SAE from treatment records, diagnostic reports, or any other source documents. If information from any relevant source documents is not available at the time of the serious adverse device event /SAE report, the relevant information will need to be added to the EDC as soon as possible.

Name of Sponsor/Company: The Albany & Saratoga Centers For Pain Management [redacted] [redacted]		
Name of Device: iovera° System		

The Investigator will follow all serious adverse device events and SAEs until resolved or the condition stabilizes, and further follow-up is not warranted.

If the Investigator is made aware of any serious adverse device event or SAEs after Day 180 that are believed to be causally related to the study device or drug treatment, these should also be reported in the EDC. The event will be followed until resolution, or until adequate stabilization is met.

Safety Endpoints:

Incidence of treatment-emergent AEs (TEAEs), including adverse device effects, serious adverse device effects, AEs, and SAEs through Day 360 (± 7 days) will collected.

The total duration of study follow-up will be 12 months after the iovera° or RFA procedure. Adverse device effects, serious adverse device effects, adverse events (AEs), and serious adverse events (SAEs) will be recorded from the time the study ICF is signed through Day 360 (± 7 days). Any concomitant medications used to treat AEs through Day 360 (± 7 days) will also be recorded.

Statistical Methods:

As the aim of this pilot study is not to assess effectiveness or efficacy, formal hypothesis testing will not be determined, and sample size will not be calculated based on desired statistical power to detect a treatment effect.

A total of 30 subjects are planned for this pilot study, with 15 randomized to each of the 2 study groups.

Descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum) will be provided for continuous data. Tabulations (number and percentage of subjects) by category will be provided for categorical data. Safety data will be summarized descriptively by treatment groups and overall, and no statistical testing for comparison of treatment groups will be performed for safety variables.

Table 1: Time and Events Schedule of Study Procedures (Day 1 - Day 180)

	Screen Visit	iovera° /RFA treatment	24h to 144h post-block Call	Day 7 Call	Day 15 Call	Day 30 Visit	Day 60 Call	Day 90 Call	Day 120 Call	Day 150 Call	Day 180 Visit
Time Window	**≤30 days pre-block**	**Day 1**	**±4h**	**±2d**	**±3d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**	**±5d**
Obtain signed ICF	X										
Assess/confirm eligibility	X	X									
Record demographics and baseline characteristics	X										
Record/update medical and surgical history	X	X									
Record/update prior/concurrent medications and therapies	X	X									
Measure vital signs[1]	X	X									
Perform physical examination per standard of care	X										
Perform neurological examination per standard of care	X										
Record NRS pain intensity scores (pain "right now")[2]	←										→
Record history of workers' compensation, personal injury, SSDI, or other litigation related to the spine	X										
Record NRS pain intensity scores (worst / average pain over 24h)	X		←								→
Administer the Oswestry Disability Index	X					X	X	X	X	X	X
Administer the PGIC						X	X	X	X	X	X
Administer iovera°/RFA treatment, record start & stop times of procedure		X									
Capture radiographic images		X									
Record concomitant medications (including opioids and analgesics)	←										→
Record subject satisfaction with pain management						X	X	X	X	X	X
Record AEs and adverse device effects (beginning at the time ICF is signed)	←										→

Abbreviations: AE = adverse event; d = day; h = hours; ICF = informed consent form; min = minutes; NRS = numeric rating scale; PGIC = Patient Global Impression of Change; RFA = radiofrequency ablation; SSDI = Social Security disability insurance

1 Vital signs will be measured after the subject has rested in a seated position for at least 5 minutes.
2 Administer pain intensity NRS prior to iovera/RFA.

Table 2: Time and Events Schedule of Study Procedures (Day 210 - 360)

	Day 210 Call	Day 240 Call	Day 270 Call	Day 300 Call	Day 330 Call	Day 30 Visit	Day 360 Call
Time Window	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**	**±7d**
Record NRS pain intensity scores (pain "right now")	X	X	X	X	X	X	X
Record NRS pain intensity scores (worst / average pain over 24h)	X	X	X	X	X	X	X
Administer the Oswestry Disability Index	X	X	X	X	X	X	X
Administer the PGIC	X	X	X	X	X	X	X
Record concomitant medications (including opioids and analgesics)	X	X	X	X	X	X	X
Record subject satisfaction with pain management	X	X	X	X	X	X	X
Record AEs and adverse device effects (beginning at the time ICF is signed)	◄						►

Abbreviations: AE = adverse event; d = day; h = hours; NRS = numeric rating scale; PGIC = Patient Global Impression of Change

LIST OF ACRONYMS/ABBREVIATIONS

AE	Adverse event
CLBP	Chronic low back pain
cm	Centimeter
COVID-19	Coronavirus disease 2019
CRF	Case report form
d	Day
DO	Doctor of Osteopathic Medicine
EDC	Electronic data capture
h	Hours
Hz	Hertz
ICF	Informed consent form
IV	Intravenous
L	Lumbar
MBB	Medial branch block
MDR	Medical device report
MED	Morphine equivalent dose
mL	Milliliter
MRI	Magnetic resonance imaging
N_2O	Nitrous oxide
NRS	Numeric rating scale
NSAIDs	Non-steroidal anti-inflammatory drugs
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
RCT	Randomized controlled trial
RF	Radiofrequency
RFA	Radiofrequency ablation
S	Sacral
SAE	Serious adverse event
SD	Standard deviation
SOC	Standard of care
SSDI	Social Security disability insurance
TEAEs	Treatment-emergent adverse events
US	United States

Appendix 1: Subject's Reported Pain (Numeric Rating Scale)

Subjects will evaluate their pain in the low back region using an 11-point Numeric Rating Scale (NRS), where 0=no pain and 10=worst possible pain.

The timepoints and assessments are as follows:

Current Pain (Pain "right now")	Daily Pain (Worst/Average pain over 24 hours)
At screening	At screening
Day of iovera° or RFA treatment (pretreatment), once daily Days 1-6 (at 6 pm ±4 hours) after treatment, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days)	Once daily Days 1-6 (at 6 pm ±4 hours) after treatment, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days)

Current Pain: Subjects will evaluate how much pain they are currently experiencing (i.e., "How much pain are you experiencing in your low back **right now**?") at Screening, day of iovera° treatment (pretreatment), once daily (at 6 pm ±4 hours) from prior to iovera° treatment to Days 1-6, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days):

Pain Intensity Scale (Current Pain)

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, circle the number that best describes your answer to the question "How much pain are you experiencing in your low back **right now**?" (Circle one number only.)

0 1 2 3 4 5 6 7 8 9 10

No pain Worst possible pain

Daily Pain: Subjects will evaluate their ***worst*** and ***average*** level of pain **over the past 24** hours at Screening, once daily (at 6 pm ±4 hours) from prior to iovera° treatment to Day Days 1-6, at Day 7 (± 2 days), Day 15 (± 2 days), Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days):

Pain Intensity Scale (Daily Pain)

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, circle the number that best describes your answer to the question "What was your **worst** pain in the past 24 hours in your low back?" (Circle one number only.)

0 1 2 3 4 5 6 7 8 9 10

No pain Worst possible pain

On a scale of 0 to 10, where 0 = no pain and 10 = worst possible pain, circle the number that best describes your answer to the question "What was your **average** pain in the last 24 hours in your low back?" (Circle one number only.)

0 1 2 3 4 5 6 7 8 9 10

No pain Worst possible pain

Appendix 2: Subject Satisfaction Assessments (Likert Scale)

Subject satisfaction with pain management will be assessed using Likert scales.

Subject Satisfaction with Pain Management

The subject's satisfaction with pain management will be conducted at Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).

Subject Satisfaction with Pain Management

Please circle the number below that best describes your overall satisfaction with your pain management. (Select one number only)

1. Extremely dissatisfied
2. Dissatisfied
3. Neither satisfied nor dissatisfied
4. Satisfied
5. Extremely satisfied

Appendix 3: Oswestry Disability Index (ODI)

Subjects will complete the ODI at Screening, Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days):

Oswestry Low Back Pain Disability Questionnaire

Instructions

This questionnaire has been designed to give us information as to how your back or leg pain is affecting your ability to manage in everyday life. Please answer by checking ONE box in each section for the statement which best applies to you. We realise you may consider that two or more statements in any one section apply but please just shade out the spot that indicates the statement which most clearly describes your problem.

Section 1 – Pain intensity

- ☐ I have no pain at the moment
- ☐ The pain is very mild at the moment
- ☐ The pain is moderate at the moment
- ☐ The pain is fairly severe at the moment
- ☐ The pain is very severe at the moment
- ☐ The pain is the worst imaginable at the moment

Section 2 – Personal care (washing, dressing etc)

- ☐ I can look after myself normally without causing extra pain
- ☐ I can look after myself normally but it causes extra pain
- ☐ It is painful to look after myself and I am slow and careful
- ☐ I need some help but manage most of my personal care
- ☐ I need help every day in most aspects of self-care
- ☐ I do not get dressed, I wash with difficulty and stay in bed

Section 3 – Lifting

- ☐ I can lift heavy weights without extra pain
- ☐ I can lift heavy weights but it gives extra pain
- ☐ Pain prevents me from lifting heavy weights off the floor, but I can manage if they are conveniently placed eg. on a table
- ☐ Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned
- ☐ I can lift very light weights
- ☐ I cannot lift or carry anything at all

Section 4 – Walking*

- ☐ Pain does not prevent me walking any distance
- ☐ Pain prevents me from walking more than 1 mile
- ☐ Pain prevents me from walking more than 1/2 mile
- ☐ Pain prevents me from walking more than 100 yards
- ☐ I can only walk using a stick or crutches
- ☐ I am in bed most of the time

Section 5 – Sitting

- ☐ I can sit in any chair as long as I like
- ☐ I can only sit in my favourite chair as long as I like
- ☐ Pain prevents me sitting more than one hour
- ☐ Pain prevents me from sitting more than 30 minutes
- ☐ Pain prevents me from sitting more than 10 minutes
- ☐ Pain prevents me from sitting at all

Section 6 – Standing

- ☐ I can stand as long as I want without extra pain
- ☐ I can stand as long as I want but it gives me extra pain
- ☐ Pain prevents me from standing for more than 1 hour
- ☐ Pain prevents me from standing for more than 3 minutes
- ☐ Pain prevents me from standing for more than 10 minutes
- ☐ Pain prevents me from standing at all

Section 7 – Sleeping

- ☐ My sleep is never disturbed by pain
- ☐ My sleep is occasionally disturbed by pain
- ☐ Because of pain I have less than 6 hours sleep
- ☐ Because of pain I have less than 4 hours sleep
- ☐ Because of pain I have less than 2 hours sleep
- ☐ Pain prevents me from sleeping at all

Section 8 – Sex life (if applicable)

- ☐ My sex life is normal and causes no extra pain
- ☐ My sex life is normal but causes some extra pain
- ☐ My sex life is nearly normal but is very painful
- ☐ My sex life is severely restricted by pain
- ☐ My sex life is nearly absent because of pain
- ☐ Pain prevents any sex life at all

Section 9 – Social life

- ☐ My social life is normal and gives me no extra pain
- ☐ My social life is normal but increases the degree of pain
- ☐ Pain has no significant effect on my social life apart from limiting my more energetic interests eg, sport
- ☐ Pain has restricted my social life and I do not go out as often
- ☐ Pain has restricted my social life to my home
- ☐ I have no social life because of pain

Section 10 – Travelling

- ☐ I can travel anywhere without pain
- ☐ I can travel anywhere but it gives me extra pain
- ☐ Pain is bad but I manage journeys over two hours
- ☐ Pain restricts me to journeys of less than one hour
- ☐ Pain restricts me to short necessary journeys under 30 minutes
- ☐ Pain prevents me from travelling except to receive treatment

Appendix 4: Patients' Global Impression of Change (PGIC)

Subjects will complete the PGIC at Day 30 (± 5 days), Day 60 (± 5 days), Day 90 (± 5 days), Day 120 (± 5 days), Day 150 (± 5 days), Day 180 (± 5 days), Day 210 (± 7 days), Day 240 (± 7 days), Day 270 (± 7 days), Day 300 (± 7 days), Day 330 (± 7 days), Day 360 (± 7 days).

Patients' Global Impression of Change (PGIC) scale.

Name: _____ **Date:** _____ **DOB:** _____

Chief Complaint: _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your painful condition? (tick ONE box).

No change (or condition has got worse)	☐	1
Almost the same, hardly any change at all	☐	2
A little better, but no noticeable change	☐	3
Somewhat better, but the change has not made any real difference	☐	4
Moderately better, and a slight but noticeable change	☐	5
Better, and a definite improvement that has made a real and worthwhile difference	☐	6
A great deal better, and a considerable improvement that has made all the difference	☐	7

In a similar way, please circle the number below, that matches your degree of change since beginning care at this clinic:

Much Better				No Change						Much Worse
0	1	2	3	4	5	6	7	8	9	10

Patient's signature: _____ **Date:** _____

Reference: Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26-35.