PROTOCOL

A Prospective, Double Blind, Randomized, Control Trial to Compare the Efficacy of Cooled Radiofrequency Ablation vs. Conventional Monopolar Radiofrequency ablation of the Geniculate Nerves for the Treatment of Chronic Osteoarthritic Knee Pain.

Sponsor:
Millennium Pain Center, LLC
1015 S. Mercer Avenue
Bloomington, IL 61701

Principal Investigator:
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Date of Protocol: 24 January 2017
Version: 1.3

The study will be conducted according to the protocol and in compliance with Good Clinical Practice and other applicable regulatory requirements.

Protocol Summary

Study Title

Prospective, double blind, randomized control trial to compare the efficacy of cooled radiofrequency ablation vs. conventional monopolar radiofrequency ablation of the geniculate nerves for the treatment of chronic osteoarthritic knee pain

Purpose of the study: To compare the efficacy of cooled radiofrequency for ablation of the geniculate nerves in the knee against the conventional monopolar radiofrequency ablation for the treatment of chronic osteoarthritic knee pain.

Objective: Demonstrate the superior efficacy of cooled radiofrequency ablation of the geniculate nerves versus conventional monopolar radiofrequency ablation in the treatment of chronic osteoarthritic knee pain.

Trial design: This is a single center randomized controlled trial. Approximately 102 patients will be randomized to one of two treatment groups. Patients with chronic knee pain, with moderate to severe osteoarthritis according to the Kellgren-Lawrence scale for at least 6 months who have failed conservative therapy will be screened for the study.
Then, patients will be enrolled based on reporting ≥50% pain relief after a fluoroscopic guided single diagnostic block of the geniculate nerves (superior medial, superior lateral, and inferior medial) with 0.5 ml of local anesthetic (2% Lidocaine).
Baseline data will be collected for all enrolled patients. Outcomes will be measured at 1, 4, 12, 24 and 52 weeks.
Outcome measures will be: Visual analogue scale (VAS) both while at rest and during ambulation, Oxford knee scores, WOMAC, and global perceived effect.

Treatment groups:
Cooled radiofrequency: Under sterile conditions, the patient will be placed in supine position on a fluoroscopic table with a pillow under the popliteal fossa. Then an anterio-posterior (AP) fluoroscopic view of the tibio-femoral joint will be obtained. Skin and subcutaneous tissues will be anesthetized using Lidocaine 1%, and a 17 gauge, 4mm active tip introducer needle provided by Kimberly Clark will be advanced percutaneously towards the junction of shaft with the epicondyle until bone contact is made, then the

needle is laterally displaced a couple of mm away from the bone. This process will be performed at the superior medial, and superior lateral aspects of the femur as well as the inferior medial aspect of the tibia. Then the fluoroscope will be placed in the lateral view to guide the depth of the needle to be at the medial third of the femur or tibia. At this point, the stylet of the introducer will be removed and the cooled radiofrequency probe will be advanced through the introducer. Following sensory and motor stimulation, cooled radiofrequency ablation will be carried out at 60 degrees Celsius for 150 seconds.

Monopolar radiofrequency: Under sterile conditions, the patient will be placed in supine position on a fluoroscopic table with a pillow under the popliteal fossa. Then an anterio-posterior (AP) fluoroscopic view of the tibio-femoral joint will be obtained. Skin and subcutaneous tissues will be anesthetized using Lidocaine 1%, and a 16 gauge, 10 mm active tip introducer needle will be advanced percutaneously towards the junction of shaft with the epicondyle until bone contact is made, then the needle is laterally displaced a couple of mm away from the bone. This process will be performed at the superior medial, and superior lateral aspects of the femur as well as the inferior medial aspect of the tibia. Then the fluoroscope will be placed in the lateral view to guide the depth of the needle to be at the medial third of the femur or tibia. At this point, the stylet of the introducer will be removed and a 100 mm radiofrequency probe will be advanced through the introducer. Following sensory and motor stimulation, radiofrequency ablation will be carried out at 80 degrees Celsius for 90 seconds.

Clinically significant pain relief will be defined as a reduction in VAS of at least 2 points.

Primary endpoint:

The primary endpoint is:

1. Mean change from baseline knee pain in VAS at 24 weeks.
   Success will be defined as a reduction in mean VAS of at least 2 points.

Secondary endpoints:

The five secondary endpoints are:

1. Functional changes as reported by the Oxford knee scores and WOMAC scores
2. Mean change from baseline knee pain in VAS at 1, 4, 12, and 52 weeks
3. Mean change from baseline knee pain in percentage of relief
4. Patient satisfaction as measured by global perceived effect

5. Incidence of adverse events

Inclusion Criteria

1. Patients who have given their written informed consent to participate in this clinical study based on voluntary agreement after a thorough explanation of the patient's participation is provided to them.
2. Female patients who are not pregnant and do not plan to become pregnant during the study. Females of child bearing potential must provide a negative pregnancy test provided by the study physician and must be using reliable contraception and must continue to use reliable contraception until study completion at 52 weeks. Non-childbearing potential is defined as postmenopausal for at least 2 years or surgical sterilization or hysterectomy at least 3 months before study start. Patients who become pregnant or who have a spouse/significant other that becomes pregnant during the course of this study agree to report pregnancy to the study physician/staff.
3. Must be older than 18 years old.
4. Must have chronic knee pain for at least 6 months.
5. Must have radiologic evidence of OA of the knee, grade 2-4 based on the Kellgreen-Lawrence scale.
6. Persistent pain despite the use of conservative treatment (physical therapy, oral analgesic, steroid injections).
7. Must have a VAS score of at least 5 with ambulation.
8. Subjects must be on a stable dose of pain medication regimen for at least 2 months.
9. ≥ 50% improvement from blocks in target knee for duration of the anesthetic

Exclusion Criteria

1. Knee pain must not be acute.
2. Previous total knee replacement
3. Evidence of connective tissue disease
4. Patients who have a BMI greater than 40.
5. Current opioid use must not be greater than or equal to 90 mg morphine equivalent per 24-hour period.

6. Evidence of serious neurological or psychiatric disorders.
7. Must not have radicular pain in the affected limb.
8. Patients with uncorrected coagulation disorders or who are on anticoagulation therapy and cannot interrupt the therapy.
9. Patients who have pacemakers or generators.
10. Patient who are pregnant, breast-feeding or women of childbearing potential with positive pregnancy tests.
11. Sexually active female patients of childbearing potential who are not willing to use adequate contraceptive measures to avoid pregnancy until week 52 of the study. Sexually active male patients who are not willing to use adequate contraceptive measures until week 52 of the study. Adequate methods of birth control include the following: Hormonal contraception (female patients) or use of at least one acceptable double-barrier method. Example: Diaphragm plus spermicidal agent or condoms (male or female) plus spermicidal agent, vasectomy, intrauterine device, and/or exclusive sexual partner for whom one of the above acceptable methods applies.
12. Patients who have cancer or a past history of any cancer within 5 years prior to the time of informed consent, with the exception of basal cell or squamous cell carcinoma of the skin.
13. Human immunodeficiency virus (HIV) infection or a clinically significant infection.
14. A clinically significant disorder such as cerebrovascular disease, pulmonary infarction, ischemic heart disease, cardiac dysrhythmia, myocardial infarction, or congestive heart failure.
15. Uncontrolled diabetes, uncontrolled pulmonary disease, or uncontrolled hypertension.
16. Patients who have evidence of major psychiatric disease, mental disorder, drug dependency, alcohol dependency, or substance abuse disorders.
17. Any patient with a medical condition and/or disease that the Investigator believes could affect the study results or the safe conduct of the study.
18. Patients who are receiving compensation according to Workers' Compensation Act or are involved in personal injury litigation.
19. Patients who participated in another clinical study within 3 months prior to the time of informed consent, or who are expected to participate in another study during the period of this study.

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SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:*

Signed: _____ Date: _____

Name
Title

** The protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site.*

LIST OF ABBREVIATIONS

AE Adverse Event

BDI Beck Depression Inventory

CRF Case Report Form

FDA Food and Drug Administration

GCP Good Clinical Practice

GPE Global Perceived Effect

IRB Institutional Review Board

OA Osteoarthritis

PI Principle Investigator

RF Radiofrequency

SAE Severe Adverse Event

VAS Visual Analogue Scale

WOMAC Western Ontario and McMaster Universities Osteoarthritis Index

1 BACKGROUND/SCIENTIFIC RATIONALE

Osteoarthritis (OA) of the knee affects 27 million adults, and in 2009 it was the fourth leading cause of hospitalization in the United States [1]. Osteoarthritis of the knee impacts 16% of the population aged 45 and older[2] and renders about 25% of the population older than 55 severely disabled[3]. Symptoms of osteoarthritis include: stiffness, pain, muscle weakness or atrophy, and loss of functionality at the affected joint. The knee is a joint that is impacted by OA more than any other joint in the body, as a result of increased weight and age[4].

Non-pharmacological treatments, such as exercise are the initial treatment course for patients in the beginning stages of OA of the knee. These typically progress to over the counter pain medications and then to other treatments, such as steroid injections. However, studies have determined that while steroid injections provide fairly rapid relief, the pain relief is short lived; lasting a few weeks[5]. A recent report from the American Academy of Orthopedic surgeons and the American Association of Orthopedic Surgeons concluded that there is inconclusive evidence to recommend the use of acetaminophen or opioid therapy as well as intra-articular corticosteroid injection for the treatment of symptomatic osteoarthritis of the knee. Furthermore, they strongly recommend, based on the available evidence, against the use of intra-articular hyaluronic acid injection and against arthroscopic lavage and or debridement of the knee[6]. Knee surgery is typically considered a last resort.

As a result of the ineffectiveness of these treatments, in the long term, a study was undertaken to determine if radiofrequency ablation of the genicular nerves of the knee provides longer lasting relief. In a prospective, double blind, randomized trial; Choi et al.[7] determined that conventional radiofrequency ablation of the genicular nerves is an effective therapeutic alternative with 59% of their patients reporting at least 50% relief. Ikeuchi et al. observed similar beneficial affect with the use of conventional radiofrequency for patients with moderate to severe knee osteoarthritis.[8] Cooled radiofrequency is another alternative to conventional radiofrequency. Cooled radiofrequency includes a cooling system that prevents localization of the generated heat at the tip of the electrode, as it is with conventional radiofrequency. Cooled radiofrequency produces larger lesion sizes than conventional radiofrequency, because of the spherical lesion shape and it allows for deeper, more symmetrical lesions[9].

Based on this evidence and clinical practice, it is hypothesized that cooled radiofrequency ablation of the genicular nerves of the knee would be a safe and effective treatment for OA of the knee. This study intends to demonstrate superior efficacy of cooled radiofrequency ablation of the geniculate nerves versus conventional monopolar radiofrequency ablation in the treatment of chronic osteoarthritic knee pain.

2 OBJECTIVES

2.1 Primary endpoint:

The primary endpoint is:

1. Mean change from baseline knee pain in VAS at 24 weeks.

Success will be defined as a reduction in mean VAS of at least 2 points.

2.2 Secondary endpoints:

The five secondary endpoints are:

1. Mean change from baseline knee pain in VAS at 1, 4, 12, and 52 weeks
2. Mean change from baseline knee pain in percentage of relief
3. Functional changes as reported by the Oxford knee scores and WOMAC scores
4. Patient satisfaction as measured by global perceived effect (GPE)
5. Incidence of adverse events

3 EXPECTED RISKS/BENEFITS

3.1 Expected risks of radiofrequency include:

- Temporary numbness
- Pain at the procedure site
- Swelling and/or bruising at the treatment site

Rarely, more-serious side effects occur, including:

- Long-term numbness

3.2 General Risks Associated with RF:

The general and most common risks associated with radiofrequency treatments are representative of a 1-2% risk to patients undergoing this procedure.[10,11] These risks are unlikely, but still possible and are outlined as follows:

3.2.1 Infections: Infections can occur during the procedure beneath the skin, or at the site of injection. Common indications of the infection can be redness, swelling, pain and fever. In severe infection, an abscess may form at the site of injection which needs surgical procedure to drain the suppuration. In any case, the infections require antibiotics for treatment.

3.2.2 Increased pain: Needles that go through skin and soft tissues may cause soreness at the site of insertion. Numbness of the skin at the site of insertion can occur. Sometimes the pain may worsen because of the muscle spasm in the area of insertion. Permanent nerve pain, though rare, can occur.

3.2.3 Damage to adjacent structures including, muscle, tendons, ligaments, nerves and blood vessels: The nerves to be lesioned may be near other structures which can get damaged.

3.2.4 Bleeding: The sticking needle may cause bleeding at the site of insertion. Though, very rare, it can be a concern when the procedure is given to patients taking aspirin or anticoagulant therapy.

3.2.5 Allergies: There is the potential of allergies or reactions to medications used during the procedure.

3.2.6 Skin burns: Skin burns can occur from dispersive or broken electrodes.

3.3 Radiofrequency lesioning contraindications:

- Infection in the overlying soft tissues at the area to be injected

- Current use of blood thinning medication (e.g. Warfarin, Heparin, Aspirin).
- Patients who do not respond to local anesthetic blocks
- Previous surgeries at the site of lesioning.
- Pregnancy
- Inability to achieve appropriate positioning.

3.4 Benefits Radiofrequency ablations are considered very safe procedures involving very minimal risk. These procedures are proven to convey a number of potential benefits on patients undergoing either form of radiofrequency. These benefits include:

- Decrease in knee pain without the complication of major surgery
- Improvement in the quality of life
- Overall patient satisfaction
- Improvement in sleep quality
- Reduction of use of oral medications

4 ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Patients who have given their written informed consent to participate in this clinical study based on voluntary agreement after a thorough explanation of the patient's participation is provided to them.

4.1.2 Female patients who are not pregnant and do not plan to become pregnant during the study. Females of child bearing potential must provide a negative pregnancy test provided by the study physician and must be using reliable contraception and must continue to use reliable contraception until study completion at 52 weeks. Non-childbearing potential is defined as

postmenopausal for at least 2 years or surgical sterilization or hysterectomy at least 3 months before study start.

4.1.3 Must be older than 18 years old.

4.1.4 Must have chronic knee pain for at least 6 months.

4.1.5 Must have radiologic evidence of OA of the knee, grade 2-4 based on the Kellgreen-Lawrence scale.

4.1.6 Persistent pain despite the use of conservative treatment (physical therapy, oral analgesic, steroid injections).

4.1.7 Must have a VAS score of at least 5 with ambulation.

4.1.8 Subjects must be on a stable dose of pain medication regimen for at least 2 months.

4.1.9 Greater than or equal to 50% improvement from blocks in target knee for duration of the anesthetic.

4.2 Exclusion Criteria

4.2.1 Knee pain must not be acute.

4.2.2 Previous total knee replacement.

4.2.3 Evidence of connective tissue disease.

4.2.4 Patients who have a BMI greater than 40.

4.2.5 Evidence of serious neurological or psychiatric disorders.

4.2.6 Current opioid use must not be greater than or equal to 90 mg morphine equivalent per 24 hour period.

4.2.7 Must not have radicular pain in the affected limb.

4.2.8 Patients with uncorrected coagulation disorders or who are on anticoagulation therapy and cannot interrupt the therapy.

4.2.9 Patients who have pacemakers or generators.

4.2.10 Patient who are pregnant, breast-feeding or women of childbearing potential with positive pregnancy tests.

4.2.11 Sexually active female patients of childbearing potential who are not willing to use adequate contraceptive measures to avoid pregnancy until week 52 of the study. Sexually active male patients who are not willing to use adequate contraceptive measures until week 52 of the study. Adequate methods of birth control include the following: Hormonal contraception (female patients) or use of at least one acceptable double-barrier method (for example: diaphragm plus spermicidal agent or condoms (male or female) plus spermicidal agent.), vasectomy, intrauterine device, and/or exclusive sexual partner for whom one of the above acceptable methods applies.

4.2.12 Patients who have cancer or a past history of any cancer within 5 years prior to the time of informed consent, with the exception of basal cell or squamous cell carcinoma of the skin.

4.2.13 Human immunodeficiency virus (HIV) infection or a clinically significant infection.

4.2.14 A clinically significant disorder such as cerebrovascular disease, pulmonary infarction, ischemic heart disease, cardiac dysrhythmia, myocardial infarction, or congestive heart failure.

4.2.15 Uncontrolled diabetes, uncontrolled pulmonary disease, or uncontrolled hypertension.

4.2.16 Patients who have evidence of major psychiatric disease, mental disorder, drug dependency, alcohol dependency, or substance abuse disorders.

4.2.17 Any patient with a medical condition and/or disease that the Investigator believes could affect the study results or the safe conduct of the study.

4.2.18 Patients who are receiving compensation according to Workers' Compensation Act or are involved in personal injury litigation.

4.2.19 Patients who participated in another clinical study within 3 months prior to the time of informed consent, or who are expected to participate in another study during the period of this study.

4.3 Subject Withdrawal

Subjects may voluntarily withdraw from the study at any time. Reasons for withdrawal will be recorded on the appropriate case report form (CRF).

4.4 Terminating Subject Participation

A subject's participation in the study may be terminated if:

1. Continued participation in the study is not in the subject's best interest, according to the Principal Investigator's opinion.

2. The subject becomes pregnant.

3. The subject withdraws participation from the study.

If the subject is terminated from the study after successful completion of the procedure, then the study coordinator will call the subject daily for one week and then once weekly for the remainder of the study period to collect data regarding Adverse Events. All attempts, whether written or verbal, will be documented and a copy placed in both the center's regulatory binder and the subject's binder. Investigators will use reasonable efforts to follow-up subjects who dropped out from the study due to an AE until resolution of the AE. Subjects who withdraw participation from the study should be asked if they will agree to be followed for easily collectable outcome data.

4.5 Changes in Study Protocol and Study Closure

The Sponsor will notify the Investigator, the FDA and the Institutional Review Board (IRB) regarding any changes to the Investigational Plan, including this Protocol, and when the study officially closes.

5 SUBJECT ENROLLMENT

5.1 Subject Eligibility and Identification: The clinical research coordinators initially screen the patient upon receiving the referral from the physician. An important prerequisite for patient recruitment into the study is that every patient should satisfy all the inclusion/ exclusion criteria. Whereas a subject should satisfy all the inclusion criteria, none of patient conditions should meet the exclusion criteria. Patients meeting these criteria are then presented with all of the information about the study, including risks and benefits at which point they are allowed to decide whether or not to proceed with screening visit. If the subject agrees to be in the study he/she is asked to sign the Informed Consent Form. Patients then undergo baseline measurements and are randomized for the study. Randomization is based on either treatment that will be applied. If a patient presents with bilateral osteoarthritis (as per inclusion criteria), then both knees will be treated using the same treatment and data will be recorded for each knee. Although prevalence of patients with bilateral knee OA is likely to be larger than that of patients with unilateral,[12,13] the number of patients with bilateral knee OA in the study will be limited to 15 per treatment group. Given that perception of pain intensity and function seems to differ between populations with unilateral and bilateral knee osteoarthritis,[13,14] the group of patients with the bilateral condition will be considered a subgroup during the analysis of the data.

6 STUDY DESIGN AND PROCEDURES

This is a single center randomized controlled trial. Approximately 102 patients will be randomized to one of two treatment groups. Patients with chronic knee pain, with moderate to severe osteoarthritis according to the Kellgren-Lawrence scale for at least 6 months who have failed conservative therapy will be screened for the study.
Then, patients will be enrolled based on reporting ≥50% pain relief after a fluoroscopic guided single diagnostic block of the geniculate nerves (superior medial, superior lateral, and inferior medial) with 0.5 ml of local anesthetic (1% Lidocaine).
Baseline data will be collected for all enrolled patients. Outcomes will be measured at 1,4,12, 24 and 52 weeks.
Outcome measures will be: Visual analogue scale (VAS) both while at rest and during ambulation, percentage of knee pain relief, Oxford knee scores, WOMAC and global perceived effect (GPE). Everyone involved in the study will be blinded to treatment, except the physician performing the procedure.

6.1 Treatment groups:

6.1.1 Cooled radiofrequency: Under sterile conditions, the patient will be placed in supine position on a fluoroscopic table with a pillow under the popliteal fossa. Then an anterio-posterior (AP) fluoroscopic view of the tibio-femoral joint will be obtained. Skin and subcutaneous tissues will be anesthetized using Lidocaine 1%, and a 17 gauge, 4mm active tip introducer needle provided by Kimberly Clark will be advanced percutaneously towards the junction of shaft with the epicondyle until bone contact is made, then the needle is laterally displaced a couple of mm away from the bone. This process will be performed at the superior medial, and superior lateral aspects of the femur as well as the inferior medial aspect of the tibia. Then the fluoroscope will be placed in the lateral view to guide the depth of the needle to be at the medial third of the femur or tibia. At this point, the stylet of the introducer will be removed and the cooled radiofrequency probe will be advanced through the introducer. Following sensory and motor stimulation cooled radiofrequency ablation will be carried out at 60 degrees Celsius for 150 seconds.

6.1.2 Monopolar radiofrequency: Under sterile conditions, the patient will be placed in supine position on a fluoroscopic table with a pillow under the popliteal fossa. Then an anterio-posterior (AP) fluoroscopic view of the tibio-femoral joint will be obtained. Skin and subcutaneous tissues will be anesthetized using Lidocaine 1%, and a 16 gauge, 10 mm active tip introducer needle will be advanced percutaneously towards the junction of shaft with the epicondyle until bone contact is made, then the needle is laterally displaced a couple of mm away from the bone. This process will be performed at the superior medial, and superior lateral aspects of the femur as well as the inferior medial aspect of the tibia. Then the fluoroscope will be placed in the lateral view to guide the depth of the needle to be at the medial third of the femur or tibia. At this point, the stylet of the introducer will be removed and a 100 mm radiofrequency probe will be advanced through the introducer. Following sensory and motor stimulation radiofrequency ablation will be carried out at 80 degrees Celsius for 90 seconds.

6.2 Screening evaluation

6.2.1 Informed Consent: Patients visiting the site with chronic knee pain for at least six months will be identified by clinic staff. Patients meeting all inclusion criteria and no exclusion criteria will be selected and referred by the investigator for the trial. The clinical research coordinator and physician will give a verbal explanation of the nature of the trial, outcome, and risks/benefits of the trial to the patients in accordance with site Standard Operating Procedures. Patient will also be provided with a written Informed Consent Form to read. Written informed consent must be obtained from the patients in order to enroll them into the trial. The informed consent document will be approved by an Ethics Committee or Institutional Review Board prior to use in the clinical trial. Research subjects will then be given a copy of the signed informed consent for their records. All patients willing to enroll in the study will be made aware of the facts that they can approach the investigator/clinical research team with any further questions at any time and that they are free to withdraw their consent and to discontinue their participation in the study at any time without prejudice. All informed consent processes are to be properly documented in accordance with the Code of Federal Regulations (45 CFR 46).

6.2.1.1 ICF Process After a patient has been identified as a potential candidate, based on the Pre-ICF screening; written Informed Consent must be obtained by asking patients to sign an Informed Consent Form (ICF).

- The context of the study must be fully explained to the patient in language that is easily understood by the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction. Study personnel should explain to each potential participant that even if he or she agrees to participate in the study and signs an ICF, further testing might demonstrate that he or she is not suitable for the study.
- Written informed consent must be recorded appropriately by means of the subject's dated signature. The consent process must be documented in the subject's medical chart.

6.2. Treatment Number Assignment, Randomization and Blinding: All patients enrolled into the study will be randomized into one of two treatment arms: Study Arm 1 (Cooled Radiofrequency) or Study Arm 2 (Conventional Monopolar Radiofrequency). Both patient and staff evaluator of data will be blinded to the treatment/procedure.

6.3 Completion of Study Procedures: Timing of study visits is given in detail in the Schedule of Evaluations included in the Protocol and Synopsis. All study visits are scheduled to fall within study visit "windows". These windows are outlined in the synopsis.

All the patients enrolled in the study should complete the study visits within the timeframes noted in the protocol. No study visits should be conducted outside of designated study visit windows. In case the subjects discontinue from the trial due to voluntary withdrawal of the consent or medical consequences, the clinical research team will complete a study exit follow-up and document all the appropriate forms. While the subject is participating in the trial, the clinical research team will maintain periodic contacts with the subjects. In cases where patients are lost-to-follow-up, all possible attempts will be made to contact the subjects including sending certified letters.

6.4 Study Procedures at each visit:

6.4.1 Screening Visit – Visit 0: Day -28 to -7

Following informed consent, the patient is screened for inclusion in the study. A physical examination will be performed by a physician and patient demographics and healthcare utilization will be collected by the clinical research coordinator.

The following information/questionnaires will be collected from the patient:

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Medical History
- Vital Signs
- Physical Examination
- Concomitant Medications
- Pregnancy Test

- Patient Global Assessment (PGA)
- Visual Analog Scale (VAS)
- Oxford Knee Score
- WOMAC
- Kellgren-Lawrence Grading Scale
- Beck Depression Inventory (BDI)

6.4.2 Baseline/Randomization Visit- Visit 1: ~7 days from Day 0

- Patient Global Assessment (PGA)
- Kellgren-Lawrence Grading Scale
- Visual Analog Scale (VAS)
- Oxford Knee Score
- WOMAC
- EQ-5D
- Healthcare utilization including any changes in Concomitant Medications
- Adverse Events

6.4.3 Treatment Visit – Visit 2: Day 0

Visit 2 may be combined with Visit 1 provided that the information that must be obtained during Visit 1 is collected prior to the interventional procedure randomly assigned to the patient (cooled radiofrequency or conventional monopolar radiofrequency). Details of the cooled radiofrequency and the conventional monopolar radiofrequency procedures are given in **Sections 6.1.1** and **6.1.2** respectively. The following information will be collected during the procedure:

- Vital Signs
- Patient Global Assessment (PGA)

- Healthcare Utilization including any changes in Concomitant Medications
- Kellgren-Lawrence Grading Scale
- Oxford Knee Score
- WOMAC
- Visual Analog Scale (VAS)
- Procedure Times (Start and Stop)
- Fluoroscopy time
- Lesioning Temperature during cooled radiofrequency
- Lesioning Time during cooled radiofrequency
- Cooled Kit Serial Number (as applicable to cooled radiofrequency)
- Cooled Probes Serial Number (as applicable to cooled radiofrequency)
- Lesioning Temperature during conventional monopolar radiofrequency
- Lesioning Time during conventional monopolar radiofrequency
- Conventional RF Kit Serial Number (as applicable to monopolar radiofrequency)
- Conventional Monopolar Probes Serial Number (as applicable to monopolar radiofrequency)
- Adverse Events

6.4.4 Study Visits- Visits 3 (1 week ± 3 days), 4 (4 weeks ± 1 week), 5 (12 weeks ± 2 weeks), 6 (24 weeks ± 2 weeks), and 7 (52 weeks ± 2 weeks): At each visit, the coordinator will collect the appropriate information as outlined below. Please note that decreases in concomitant pain medications are permitted post-treatment and should be tracked at each visit as an outcome measure of the study. All the data will be entered into appropriate CRFs.

- Vital Signs
- Patient Global Assessment (PGA)
- Kellgren-Lawrence Grading Scale
- Oxford Knee Score
- WOMAC
- Healthcare Utilization including any changes in Concomitant Medications
- EQ-5D
- Visual Analog Scale (VAS)
- Changes in Pain Medication
- Adverse Events

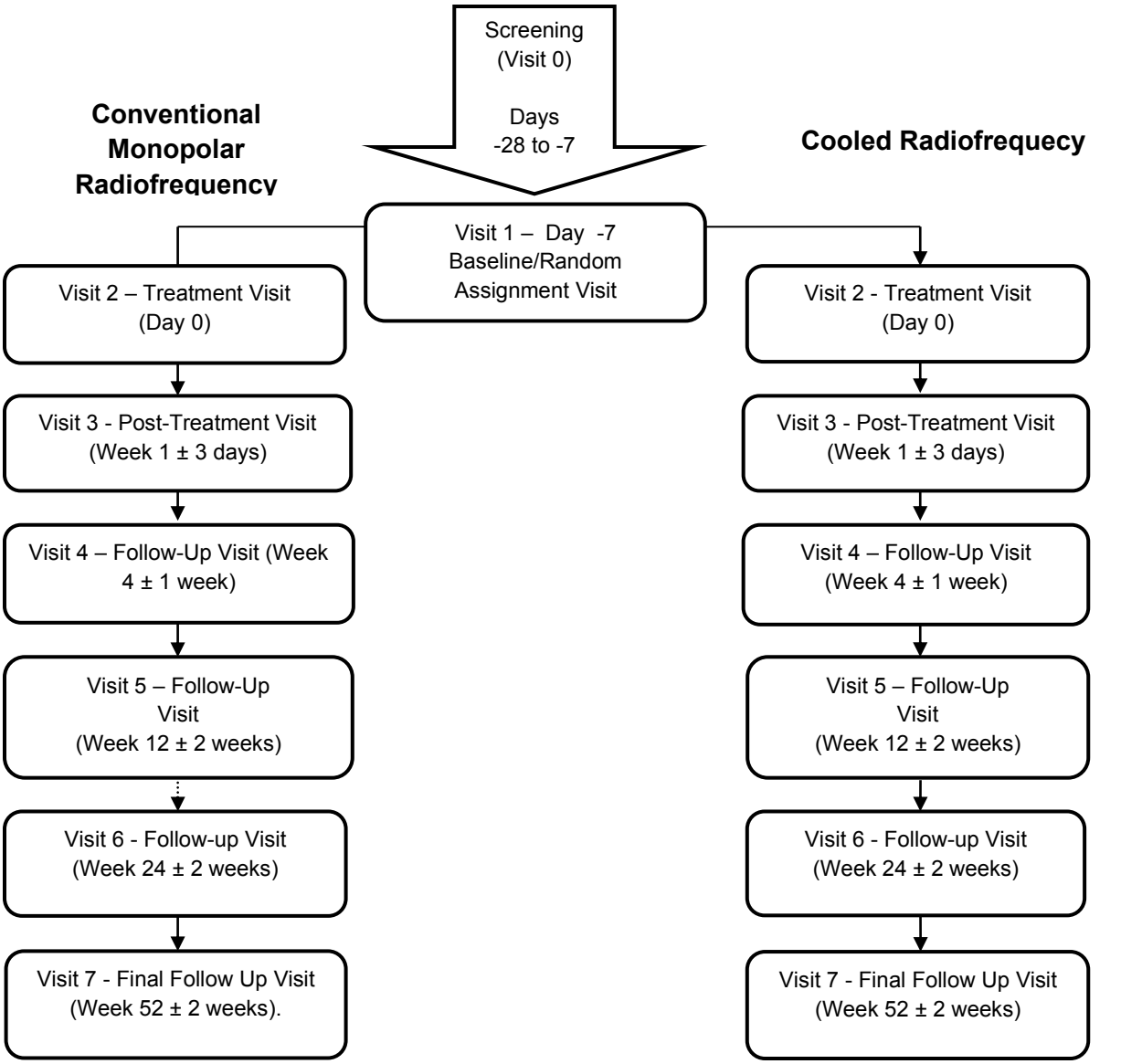

Figure 1: Schedule of visits

7 PRODUCT INFORMATION

7.1 Kimberly Clark Cooled RF Pain Management System There are five primary components to the cooled radiofrequency kit, which include, the probe, introducer, peristaltic pump unit, tube kit and generator.

7.1.1 Pain Management Radiofrequency Probe

- Probe includes a 4-foot connecting cable and tubing extension to reach out of the sterile field. These are connected to the generator and peristaltic pump unit for RF energy delivery and internal cooling.
- A thermocouple in the probe measures cooled electrode temperature throughout the procedure.
- A radiopaque marker is located at the proximal end of the active tip. This marker defines the lesion location under fluoroscopy, confirming position and enhancing visualization.

7.1.2 Pain Management Introducer

- The sterile, single use introducer provides a path for the probe to the nervous tissue.

7.1.3 Pain Management Cooled RF Peristaltic Pump Unit

- The pump unit is used to circulate sterile water to the radiofrequency probe tip during lesion formation.

7.1.4 Pain Management Tube Kit

- The sterile, single use tube kit is used for closed-loop circulation of sterile water through the probe. It includes a burette to hold water, connected to tubing that is inserted in the pump unit.

7.1.5 Pain Management Radiofrequency Generator

- The Kimberly-Clark Pain Management Generator PMG-115-TD or PMG-230 (V. 2 or higher) are the only radio frequency generators compatible with Kimberly-Clark Cooled-RF Pain Management Systems.

7.2 Kimberly Clark Conventional Monopolar RF Pain Management System There are three primary components to the monopolar radiofrequency kit, which include the probe, introducer, and generator.

7.2.1 Pain Management Radiofrequency Probe

- Probe includes a 4-foot connecting cable to reach out of the sterile field. This is connected to the generator for RF energy delivery.

- A thermocouple in the probe measures the electrode temperature throughout the procedure.

- A radiopaque marker is located at the proximal end of the active tip. This marker defines the lesion location under fluoroscopy, confirming position and enhancing visualization.

7.2.2 Pain Management Introducer

- The sterile, single use introducer provides a path for the probe to the nervous tissue.

7.2.3 Pain Management Radiofrequency Generator

- The Kimberly-Clark Pain Management Generator PMG-115-TD or PMG-230 (V. 2 or higher) are the only radio frequency generators compatible with Kimberly-Clark Conventional Monopolar-RF Pain Management Systems

8 DATA ANALYSIS

8.1 Sample size. A sample size of 44 in each group will have 80% power to detect a difference in means of 1.5 in VAS assuming that the common standard deviation is 2.54[5] using a one-way ANOVA approach with a 5% two-sided significance level. Considering an attrition rate of 15%, 51 subjects per group, a total of 102 subjects ought to be enrolled into the study.

8.2 Randomization: Patients enrolled into the study are randomized to either Cooled Radiofrequency group or Conventional Monopolar Radiofrequency group using randomization envelopes. Randomization will occur at the baseline visit.

8.3 Analysis Plan: The efficacy of Cooled Radiofrequency ablation vs. Conventional Monopolar Radiofrequency ablation of the geniculate nerves for the treatment of chronic osteoarthritic knee pain will be compared. Thus, the following hypotheses will be tested:

$$H_0: \mu 1 = \mu 2$$

$$H_1: \mu 1 \neq \mu 2$$

Where, μ1 = Mean VAS score from baseline at 24 weeks from cooled-radiofrequency and μ2 = Mean VAS score from baseline at 24 weeks from conventional monopolar radiofrequency.

Follow-up evaluations (Follow-Up Schedule, Section 6.4) will be summarized using descriptive statistics on physical exams, questionnaires evaluating pain, disability, function (activity), overall health status, analgesic medication usage, overall patient impression of change, treatment satisfaction, psychological factors and adverse event reporting.

An interim analysis will be carried out when 21 subjects in each treatment group complete 24 weeks in the study in order to evaluate the efficacy of the treatments relative to baseline. If at this point the mean difference of VAS scores is larger than 2.5 with a standard deviation of 2.8 or less then the results will be statistically significantly different at 80% power and 5% two-sided significance level based on a one-way ANOVA approach. In this case the study may be closed to enrollment and be continued to complete treatment and follow-up with the patients already enrolled.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Sponsor Millennium Pain Center will serve as the Sponsor of this clinical investigation. It is the responsibility of Millennium Pain Center as the Sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met. The study will be conducted under Good Clinical Practice (“GCP”) guidelines and applicable regulatory requirements. All data used in the analyses and reporting of this investigation will be coded without identifiable reference

to the subject. Access to these confidential files will be given to only authorized personnel and representatives of the Sponsor and regulatory authorities as required.

9.2 Data Collection Study records are comprised of source documents, electronic and paper patient diaries (ePROs), medical records, electronic and paper Case Report Forms (CRFs), and all other administrative documents, e.g., IRB correspondence, clinical trial materials and supplies shipment manifests, monitoring logs, Sponsor correspondence, etc. A study-specific binder will be provided with instructions for maintenance of study records.

Source documentation is defined as any hand-written or computer generated document that contains medical information or test results that have been collected for or is in support of the protocol specifications, e.g., lab reports, clinic notes, subject completed questionnaires, telephone logs, etc. A CRF may serve as a source document. All draft, preliminary and pre-final iterations of a final report are also considered source documents, e.g., faxed lab reports and hard copy lab reports, faxed initial results and hard copy final report.

9.3 Record Retention Site records of the study (e.g., protocol, correspondence with Sponsor and IRB, IRB approvals, source documentation, patient records, consents, and reports) must be maintained by the Investigator until further notification from Millennium Pain Center and for as long as local document retention regulations require, which is minimally for a period of two years after the investigation is completed or terminated. If an Investigator withdraws from the study (e.g., because of relocation), then the records will be transferred to a mutually agreed upon designee (i.e., another Investigator). This transfer is subject to Millennium Pain Center approval and will be documented in writing and a copy sent to Millennium Pain Center. Should the Investigator leave the site at which the study was conducted, the Sponsor will be contacted regarding the disposition of documents.

9.4 Inspection of Records In the event of an audit, the Investigator agrees to allow representatives of Millennium Pain Center, the Food and Drug Administration, National Health Authorities, or other regulatory authorities, access to all study records as required.

10 STATISTICAL CONSIDERATIONS

Based on previous studies showing 60% of patients achieving the primary outcome with conventional radiofrequency, the ANOVA sample size for the present study, considering an active group and including an estimated 15% attrition was calculated at 51 patients per group/arm. The sample size calculation assumed a minimal detectable difference in means of 1.5 (clinically significant) and a common standard deviation of 2.54 at a power of 80% for a two tailed α value of 0.05.

11 REGULATORY REQUIREMENTS

11.1 Institutional Review Board Approval: All the documents related to the study, such as protocol, Informed Consent Form, CRF should be submitted by the investigator to an appropriate Institutional Review Board for review and approval before initiation of the study. The investigator requests the board to provide a written approval of all the documents used during the study. In case, any member of the investigation team or the investigator is a member of the Institutional Review Board, they must not participate in the review of the documents or decision making. Following initial approval of the protocol and other documents used for the study by the Institutional Review Board, any subsequent changes made to the study documents should be notified to the Review Board and get approved. All subsequent approvals from the Board should be in a written form and filed with the original study documents.

Investigator should notify Institutional Review Board about occurrence of any serious adverse event within 24 hours of the incidence.

11.2 Informed Consent: Before patients are enrolled into the study, investigator or the clinical research team member should explain purpose, procedure and possible outcome of the study to each patient. After understanding about the study in detail, each patient should give voluntary, written consent to participate in the study through signing on the Informed Consent Form. The investigator signs on the Informed Consent Form after it is signed by the patient. Original copy of the duly signed Informed Consent Form is retained with the investigator file at the study site. One copy of the signed Informed Consent Form is kept in the patient notes maintained at the investigation site and patient receives one copy of the signed Informed Consent Form.

11.3 Confidentiality of the Subject Records: Investigator/clinical research team should maintain confidentiality of subject data at all times during the entire investigation. At the time of enrollment of patients for the trial, each patient is assigned a unique trial number and subject anonymity is maintained on all study-related documents by addressing the subject using trial number in the place of the name of the subject. All procedural notes pertinent to the study will be de-identified to maintain subject anonymity. All the study documents and data will be kept in secure locations with locks. All computers containing patient information and study related data will be password protected, with authorized users having access to the information contained on them and in limited access areas.

11.4 Good Clinical Practices: Present investigation will be carried out by strictly following all applicable clinical trial regulations and good clinical practices.

11.5 Investigational Personnel and Responsibilities: Before the initiation of the investigation, Principal Investigators from both the sites will approve the written protocol by signing on the signature page. The signature of the principal Investigator ensures that the trial will be performed in compliance with the protocol. Subsequently, the study will be conducted as per the approved protocol without deviations from protocol at any point of the study.

11.6 Case Report Form Completion: During the entire study, the investigation team collects data as accurate as possible from each subject enrolled in the study. All the entries will be recorded on the CRFs or source documents using ink. Any errors during the entry of the data into the CRFs or source documents should be crossed out with single stroke, initialed and dated. Typing correction fluid will never be used in any type of study document. Personal data recorded in any of the study documents will be considered confidential. Investigators will be responsible for the timing, completeness and accuracy of the record forms and will retain a copy of each completed form.

Subject's source documents are maintained separately for each patient participating in the trial. In addition to the source documents, a separate list of all patients enrolled into the study is maintained containing each subject's name, date of birth and assigned subject number (this list is used for identification purpose). Apart from the list of patients, subject identification log is included into the Investigator Regulatory Binder at the study site to record the subject's initials, date of birth and assigned subject number.

11.7 Adverse event reporting: An adverse event during medical treatment is defined by the FDA as "Any unfavorable, unintended sign, symptom or disease associated with the use of a medical product, whether or not considered related to the product". A list of potential adverse events and adverse device effects, which may be associated with this investigation, will be included in the protocol.

Detailed information about any adverse event occurred during the study will be enclosed in the appropriate CRF. The details include nature of adverse event, date of onset, duration, severity, possible association with the treatment. The adverse event will be followed by the clinical research team and investigator until the medical condition is completely resolved. Following an adverse event, the concerned patients will be questioned in detail about the recurrence of any symptoms related to the adverse event at each subsequent visit and all details will be recorded in appropriate CRFs.

Adverse events are usually unexpected, and can be categorized as mild, moderate or severe. Adverse event is considered serious when it meets following conditions:

- Life threatening or fatal
- May permanently incapacitate or disable patient
- Require in-patient hospitalization (≥24 hours) because of potential disability, danger to life of needs medical intervention

All serious adverse events (SAE) that may occur during the investigation should be reported within 24 hours by telephone or facsimile to research site's IRB.

The investigator should initiate appropriate therapeutic and follow-up measures in accordance with good medical practice and also notify the study monitor about the occurrence of adverse event, measures taken to resolve the event. All the details about the adverse event should be entered into subject's CRF by the study monitor.

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