NCT03491397

Protocol Title:	**Feasibility of genicular artery embolization (GAE) for the treatment of pain associated with symptomatic knee osteoarthritis**
IDE Number:	**G180048**
Sponsor/Investigator:	**Siddharth A. Padia, MD** **University of California, Los Angeles** **1245 16th St.** **Suite 100** **Santa Monica, CA 90404** **(310) 319-3352**
Date of Protocol:	**March 13, 2020**
Protocol Version:	**1.10**

TABLE OF CONTENTS

1. Introduction

Background: osteoarthritis

Osteoarthritis (OA) is the most common degenerative joint disease and a leading cause of chronic pain and physical disability in older individuals. The lifetime risks of developing symptomatic knee OA are estimated at 40% in men and 47% in women (1).

The hallmark symptom of OA is pain. This is the symptom that drives individuals to seek medical attention and contributes to functional limitation and reduced quality of life (2); the alleviation of pain is the main motivation for treatment, including nonpharmacologic, pharmacologic, and surgical approaches. End-stage knee OA is successfully treated with joint replacement surgery, but effective management of mild to moderate radiographic knee OA refractory to conservative treatment can be difficult.

Although OA was viewed as a "wear-and-tear" disease for many decades, it is now generally accepted to be a low- grade inflammatory disease of synovial joints and a biomechanical whole-organ disease (3). Angiogenesis is believed to contribute to the genesis of inflammation and particularly to its maintenance (4). The new increased vascular network provides inflammatory cells access to the synovium and other joint tissues and promotes additional hyperplasia and inflammation in other vessels, leading to bone and cartilage destruction (4). In addition, studies on OA have shown that angiogenesis may contribute to chronic pain by enabling the growth of new unmyelinated sensory nerves along their path (5).

Selective genicular artery embolization (GAE) is an innovative, minimally invasive procedure that involves catheterization of the genicular artery and partial occlusion of this vessel (embolization) with particles. Preliminary data from feasibility studies in humans have been completed and show an excellent safety profile and efficacy (6, 7). The desired effect is to decrease vascularity, leading to a reduced inflammatory response. The purpose of this investigation is to confirm the safety and efficacy of GAE in adults with knee OA.

Background: embolization

The concept and practice of therapeutic arterial embolization is over 50 years old. Embolization has traditionally been used to treat acute hemorrhage (e.g. embolization of the gastroduodenal artery for gastrointestinal hemorrhage). Over the past twenty years, the practice of embolization has evolved to treat patients with both benign and malignant tumors. For example, liver cancer is now routinely treated via embolization of the hepatic artery (8). Benign symptomatic uterine fibroids are typically treated with particle embolization of the uterine arteries in the pelvis (9). Uterine fibroid embolization now has level I evidence as a treatment option by the American College of Obstetricians and Gynecologists for patients with symptomatic uterine fibroids (10).

Embolization of arteries in the musculoskeletal system is typically performed in the setting of trauma in order to stop ongoing hemorrhage or for pre-operative embolization of hypervascular tumors. Treatment of bleeding arteries was quickly recognized as one potential therapeutic application of arterial embolization in the knee. Several reports of genicular artery embolization for the treatment of hemarthrosis after knee surgery have shown to result in significant symptomatic clinical improvement (11, 12).

Rationale
The knee receives its blood supply from the genicular arteries, branches from the superficial femoral and popliteal arteries. Deliberate partial blockage of the genicular arteries (embolization) leads to reduction of the inflammatory response, with potential improvement in pain.
Recently, Okuno and colleagues reported their experience with genicular artery embolization for patients with mild-to-moderate knee osteoarthritis. In their pilot study, 14 patients underwent embolization (7). No major adverse events were reported. There was a dramatic and rapid reduction in symptom and pain scores of patients.

In 2017, the same authors reported their results of genicular artery embolization performed on 95 knees in 72 patients (6). All patients had pain that was resistant to conservative treatment, such as oral nonsteroidal ant-inflammatory drugs, oral opioid agents, physical therapy, stretching, muscle strengthening, or intraarticular injection of hyaluronic acid. The distribution of local tenderness (indicating the presence of inflammation) was evaluated in all cases immediately before transcatheter arterial embolization and subdivided into eight areas to determine the key arteries to be treated. After selective catheterization of the appropriate genicular artery, imipenem/cilastatin sodium was used as the embolic material in 88 knees in 65 patients. Patients who had contraindications to imipenem/cilastatin (ie, a history of hypersensitivity or allergy to antibiotic agents or treatment with valproic acid) were treated with 75-μm Embozene microspheres instead (7 knees in seven patients).

Mean Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores decreased significantly from 12.1 at baseline to 6.2 at 1 month, 4.4 at 4 months, 3.7 at 6 months, 3.0 at 12 months, and 2.6 at 24 months after the first transcatheter arterial embolization procedure (all $P < .001$). The intent-to-treat clinical success rate at 6 months of follow-up was 86.3% (95% CI, 78%–92%). The mean total WOMAC score also decreased significantly from 43 at baseline to 24, 14.8, 11.2, 8.2, and 6.2 at 1, 4, 6, 12, and 24 months, respectively (all $P < .001$). The mean VAS score significantly decreased from 72 at baseline to 38, 29, 19, 13, and 14 at 1, 4, 6, 12, and 24 months, respectively (all $P < .001$). Patients reported a decrease in the dose of medication used and frequency of other treatments after the procedure.

No serious adverse events were noted. Minor complications occurred, such as moderate subcutaneous hemorrhage at the puncture site and transient cutaneous color change on the treated knee, all of which resolved without treatment.

While these single center results show a great deal of promise, the vast majority of patients underwent embolization with imipenem/cilastatin, which is not readily available in the United States. Seven patients underwent embolization with small calibrated microspheres (75-μm Embozene, Boston Scientific). While equivalent success rates were shown between the two embolics, the low number of patients treated with Embozene microspheres precludes a true comparative analysis.

Embozene particles are FDA approved for the embolization of hypervascular tumors and arteriovenous malformations. Several studies have shown excellent safety and efficacy with regards to tumor control and objective response in liver cancer (13, 14). It has been used extensively for the treatment of symptomatic uterine fibroids, where Embozene embolization of the uterine arteries results in necrosis of uterine fibroids and cessation of abnormal vaginal bleeding (9). Other proven uses include embolization of arteriovenous malformations and fistulas (15).

Genicular artery embolization appears to be safe and effective for the treatment of knee osteoarthritis based on a single center study. Its mechanism of action in decreasing knee hypervascularity and inflammation appears consistent with other studies. Embozene particles are FDA-approved for the treatment of hypervascular tumors, and have shown promise in this arena. Based on these principles, a study of the safety and efficacy of Embozene particles for genicular artery embolization is warranted.

2. Study Objectives

2.1 Primary Objective

The primary objective of this investigation is to assess safety of genicular artery embolization (GAE) for knee osteoarthritis (OA) using Embozene particles.

2.2 Secondary Objectives

The secondary objectives of this investigation are to assess efficacy using the following outcomes, compared to baseline values when appropriate:

- Improvement in pain
- Improvement in WOMAC score
- Change in radiographic imaging

3. Eligibility Criteria

3.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria in order to be eligible for this study:

- Provided informed consent
- Age ≥ 40 years and less than 80 years
- Life expectancy greater than 12 months
- Ineligibility for or refusal of surgical management
- Moderate-severe knee pain as determined by visual analog scale $\geq$ 4
- Osteoarthritis based on xray. Kellgren-Lawrence score $\geq$ 1 based on radiograph completed within 6 months of procedure date.
- Local knee tenderness
- Resistant/failed conservative treatment (e.g. NSAIDS/physical therapy/steroid joint injection) for at least 3 months.

3.2 Exclusion Criteria

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

- Mild knee pain as determined by visual analog scale < 4
- Chronic renal insufficiency (serum creatinine >2 mg/dL)
- Uncorrectable bleeding diathesis
    - INR >1.6
    - Platelets <50,000
- Significant arterial atherosclerosis that would limit selective angiography
- Allergy to iodinated contrast agents that is not responsive to steroid management
- Active Infection or malignancy
- Appropriate candidate for knee replacement surgery determined by clinical and physical examination
- Recent (within 3 months) or active cigarette use
- Prior knee arthroplasty surgery in the subject knee
- Active pregnancy

4. Study Design

This is a single-center, prospective, single arm investigational study to evaluate the safety of genicular artery embolization (GAE) for treatment of symptomatic knee osteoarthritis (OA). In addition, the improvement as part of efficacy will be reported. All subjects will have either failed or be intolerant to conservative management, and be ineligible for or refuse surgical intervention. Subjects will be considered enrolled in the study once they have provided informed consent and have been determined to meet all eligibility criteria. A total of 40 subjects will be enrolled in the single treatment arm of the study and will be followed for 12 months. The subjects will be stratified according to arthritis severity based on imaging, with 20 subjects allocated to mild-moderate arthritis based on x-ray (Kellgren-Lawrence x-ray grade 1-2), and with 20 subjects allocated to severe arthritis based on x-ray (Kellgren-Lawrence x-ray grade 3-4). The stratification will not be randomized, but each category will be limited to 20 patients.

The study will involve a screening period in which patient eligibility is determined. Once eligibility is confirmed, subjects will undergo GAE with Embozene microspheres (100 micron). Following treatment, subjects will return for follow-up visits at 1 week (± 4 days), 1 month (± 2 weeks), 3 months (± 2 weeks), 6 months (± 2 weeks), and 12 months (± 2 weeks) post-procedure. At these visits, subjects will complete the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, and a visual analog scale (VAS) score, undergo a directed physical examination, and report any new adverse events (AEs). At 3 months of follow-up, subjects will also undergo knee MRI. At 12 months of follow-up, subjects will also undergo knee x-ray. At the 12 month follow-up, subjects will also complete a patient-reported outcomes (PRO) and patient global impression of change (PGIC) questionnaire.

The primary objective of the study will be to assess safety via minor and major adverse events. Secondary objective will be improvement of OA symptoms as assessed by the WOMAC and VAS scores at each follow-up visit. Subjects will continue to be followed according to the institutional standard of care after they complete the 12-month study visit.

5. Treatments and Assessments

Subjects will be treated with a genicular artery embolization (GAE) procedure performed with Embozene Microspheres. The microspheres will be delivered in a saline-contrast medium solution and will be delivered to the arteries supplying the areas of the subject's pain. A complete description of the technical protocol to be followed is provided in Appendix C.

After GAE, follow-up visits will take place at 1 week (± 4 days), 1 month (± 2 weeks), 3 months (± 2 weeks), 6 months (± 2 weeks), and 12 months (± 2 weeks) from the date of treatment. Subjects who cannot present in person to the clinic at the 3, 6 or 12 month visit due to travel restrictions from the COVID-19 virus will conduct the follow-up visit over the phone. A schedule of study events and study flow chart are presented in Appendices A and B, respectively.

5.1 Visit 1: Screening/Baseline (within 8 weeks of GAE)

Subjects that meet all eligibility criteria listed in Section 3 above are eligible for participation in this study.

Prior to enrollment, each patient will have the following assessments performed:

- Obtain written informed consent
- Medical history, including demographics
- Physical examination including vital signs
- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1) questionnaire
- Visual analog scale (VAS) score
- Laboratory evaluation: serum complete blood count and basic metabolic panel
- Knee MRI without contrast. If patients cannot undergo MRI (e.g. pacemaker, significant claustrophobia), then CT of the knee without contrast will be performed. If a knee MRI or CT has already been performed within 6 months of Visit 1, that will be accepted.
- Knee x-ray (within 6 months of Visit 1)
- Evaluation for moderate sedation

5.2 Visit 2: Genicular Artery Embolization

The following data will be collected during each GAE procedure:

- Technical success of GAE, defined as successful catheterization and embolization
- Procedure time, duration of hospitalization, duration of catheterization, fluoroscopy dose, volume of embolic delivered, arteries embolized.

5.3 Visits 3-7: Post GAE Follow-Up

Subjects will have the following assessments performed:

- Physical examination including vital signs
- WOMAC and VAS questionnaires (at visits 4-7)
- Review of adverse events
- Knee MRI (at visit 5: 3 month follow-up). If patients cannot undergo MRI (e.g. pacemaker, significant claustrophobia), then CT of the knee without contrast will be performed.
- Knee x-ray (at visit 7: 12 month follow-up)

6. Withdrawal of Subjects

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse Event
- Concurrent medical condition
- Patient unwillingness to comply with study requirements
- Patient death
- Other Investigator decision

If a patient is withdrawn or discontinued from the study, the reason for withdrawal will be recorded in the source documents and on the End of Study case report form (CRF). All patients withdrawn from the study will be encouraged to complete, if possible, all clinical evaluations scheduled for the 12-month follow-up visit. All adverse events will be followed as described in Section 7. Patients who are withdrawn from the study for any reason will not be replaced. The Principle Investigator may terminate the study at any time.

7. Adverse Events

7.1 Definitions

Adverse Event: An adverse event (AE) is any untoward medical occurrence in a patient regardless of any causal relationship with a study treatment or procedure. An AE can therefore be any unfavorable or unintended sign, symptom, or disease temporally associated with the use of a medicine or a procedure, whether or not considered related to the product or procedure. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for a serious adverse event as defined below.

Laboratory data will be collected as described in this protocol. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate.

Patients will be instructed to report AE that they experience to the Investigator or Study Coordinator at each visit. AEs occurring during the trial and the protocol-defined 12-month follow-up period will be reported on the AE case report form (CRF). The Investigator will record AE terms according to Medical Dictionary for Regulatory Activities (MedDRA) lowest level terms. Whenever possible, a specific disease or syndrome will be reported rather than the associated signs and symptoms. Independent signs and symptoms will be reported as separate AEs.

All AEs will be assessed for severity, relationship to the study treatment, treatment required and outcome/resolution. This information will be reported on the AE CRF.

Serious Adverse Event: A serious adverse event (SAE) is any AE, occurring at any dose and regardless of causality, that:

- Results in death
- Is life-threatening, such that the patient was at immediate risk of death from the event as it occurred
- Requires inpatient hospitalization or prolongation of existing hospitalization; note that hospital admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease was diagnosed before the patient was enrolled in the study (provided that the patient's condition does not deteriorate in an unexpected manner during the study)
- Results in persistent or significant disability or incapacity, such that the patient experiences a substantial disruption of their ability to perform normal functions
- Is an important medical event as determined by the Investigator. An important medical event is an event that may not result in death, be life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Under this protocol, scheduled hospitalizations or elective surgical procedures will not be considered SAEs. Complications associated with surgical procedures or study treatments resulting in one of the outcomes above are considered SAEs.

7.2 Adverse Event Reporting

The Investigators are responsible for monitoring the safety of patients who have been enrolled in the study. All AEs considered to be related to the procedure or study device will be followed

until the event resolves or has reached a fatal outcome. AEs will be evaluated for severity using the standardized terms "mild," "moderate" and "severe."

The Investigators will document all AEs occurring during the study, commencing with the date of the GAE treatment and including the protocol-defined 12-month follow-up period. AEs and SAEs that occur following the signature of informed consent but prior to treatment will not be captured or reported.

7.3 Serious Adverse Event Reporting

Any unanticipated SAE, including death due to any cause that occurs during the study treatment or initial 12-month follow-up period, related to the procedure or study device, will be reported to the FDA within 3 days of the site learning of the event.
Unrelated SAEs will be reported at the FDA IDE annual report. The SAE must be completely described on the AE CRF as well as the Serious Adverse Event Form.

All safety concerns should be reported to:

Siddharth Padia, MD
1245 16th St.
Suite 100
Santa Monica, CA 90404
spadia@mednet.ucla.edu
310-319-3352

7.4 Potential adverse events

Commonly observed

Blood draw:
- Temporary pain from the needle stick
- Bruising or swelling at the site

MRI:
- Feeling of claustrophobia

Angiogram:
- Temporary pain at the insertion site

Genicular artery embolization:
- Temporary discoloration of the skin (less than 2 weeks)
- Temporary soreness in the knee (less than 2 weeks)

Less likely

Blood draw:
- Fainting

Angiogram:

- Allergic reaction to contrast dye
- Reaction to sedative medications (for example: nausea, itching)

Rare but serious

Blood draw:
- Infection

MRI:
- Potential heating or movement of any metal in the body

Angiogram:
- Possible risk of a blood clot in the artery
- Bleeding around the catheter insertion site
- Damage to the artery itself.
- Risk of ionizing radiation (typically less than a CT scan)

Genicular artery embolization:
- Infection
- Prolonged severe pain
- Injury to the knee (osteonecrosis)
- Allergic reaction to Embozene Microspheres
- Sequela of non-target embolization (skin necrosis, toe necrosis).

Warnings/complications on the Embozene Microsphere IFU include:

- Undesirable reflux or passage of Embozene into normal arteries adjacent to the target or through the lesion into other arteries or arterial beds.
- Embolization of the wrong artery or migration of the microspheres to other parts of the body, which may necessitate further treatment.
- Hematoma, or bruising, at the incision site for arterial access.
- Arterial aneurysm or thrombosis at the incision site for arterial access.
- Deep vein thrombosis, or clotting of a deep vein in patient's leg.
- Pulmonary embolization
- Ischemia at an undesirable location
- Capillary bed saturation and tissue damage.
- Ischemic stroke or ischemic infarction
- Vessel or lesion rupture and hemorrhage
- Neurological deficit including cranial nerve palsies.
- Vasospasm
- Recanalization
- Foreign body reactions necessitating medical intervention
- Infection necessitating medical intervention
- Clot formation at the tip of the catheter and subsequent dislodgement
- Allergic reaction
- Risks of radiation from angiography and fluoroscopy used to visualize the blood vessels during embolization, which may include a radiation burn and risks to future fertility.
- Death

Many of these risks may not apply, since these risks are from embolizing areas in the lungs or brain.

Every effort will be made to minimize risks of the procedure. Since the embolization is being performed in a branch off of the femoral or popliteal artery in the knee, many of the risks listed on the IFU do not apply to the intended use in the protocol. For example, "migration of the microspheres to other parts of the body" cannot occur since the procedure is being done in an extremity, unlike a liver embolization for liver tumors where collateral vessels are present. The use is for arterial embolization, and deep vein thrombosis or pulmonary embolism only occurs in the setting of Embozene embolization of a vascular malformation, where there is an inherent abnormal communication between arteries and veins. Ischemic stroke or neurological deficit should only occur if embolization is being performed in the head or neck, and since the embolization is being performed in the knee, this risk does not apply. The risks of radiation from this procedure is exceedingly low, since angiography is only being performed on the extremity. Therefore, vital solid (eyes, thyroid) and reproductive organs (ovaries, testicles) are not in the field of view. Angiography of the extremity tends to involve extremely low amounts of radiation due to the lack of fat and muscle (compared to the abdomen) needed to penetrate for the x-rays. Finally, death from the use of this device has only been reported in embolization of high-risk regions, such as the lungs or brain. Since the procedure is being performed in the knee, there is no risk of death in this study.

An MRI (or CT) of the knee will be performed during follow up, for the purposes of detecting any sequela of non-target embolization, or other unexpected abnormality. It is likely that there will be no changes in the MRI or CT appearance compared to baseline.

8. Symptom Assessment

8.1 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1)

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a widely used, set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. It can be self-administered and was developed at Western Ontario and McMaster Universities in 1982.

The WOMAC measures five items for pain (score range 0–20), two for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). Physical functioning questions cover everyday activities such as stair use, standing up from a sitting or lying position, standing, bending, walking, getting in and out of a car, shopping, putting on or taking off socks, lying in bed, getting in or out of a bath, sitting, and heavy and light household duties.

A WOMAC test takes about 12 minutes, and is among the most widely used assessments in arthritis research.

A copy of the WOMAC (version 3.1) is provided in Appendix D.

8.2 Visual analog scale (VAS)

The VAS is a validated commonly used pain score. A copy of the VAS score is provided in Appendix E.

8.3 Patient-reported outcomes (PRO) and patient global impression of change (PGIC)
The patient-reported outcomes (PRO) and patient global impression of change (PGIC) questionnaire is provided in Appendix G.

9. Statistical Analysis

Safety Analyses
Cumulative rates of AEs will be estimated and 95% CIs will be reported. AEs will be analyzed as a composite of all AEs, composites based on major AE types or severity and as individual AE types. The rates will be compared qualitatively to values reported in the literature of other studies of GAE and knee arthroplasty. An interim safety analysis will be performed after the first 10 patients are treated.

With 40 patients expected with the stratification of moderate and severe arthritis, we can achieve approximate 83% power to test the difference of 10% of the upper bound of a 95% CI for an AE rate of <0.01% (no such events seen) vs 10%. At this sample size, for AE rates of 0% to 50%, the difference between the upper bound of the 95% CI and the estimate AE rate ranges from 7.1% to 14.8%. These calculations were based on exact binomial CIs, assuming no loss to follow up.

Efficacy Analyses
The primary is the change in WOMAC before GAE to 12 months after GAE. All statistical tests and confidence intervals (CIs) will be two-sided with a nominal significance level of $p < 0.05$ (95% confidence). A linear mixed model (LMM) will be used to test for the mean change in WOMAC while adjusting for potential site-effects. The baseline and 12 month observations will be included in the model. The dependent variable will be the changes in WOMAC and the independent variables will be the WOMAC at baseline, baseline severity (moderate/severe arthritis), indicators of time (fixed effect Δ) and random intercepts for patient and site. The parameter Δ corresponds to the mean change in WOMAC. A Wald-type test of $\Delta = 0$ and 95% CI of Δ will be calculated.

Secondary analyses will also include analyzing changes from baseline to other timepoints and between post-treatment timepoints using the same methods. The Kaplan-Meier curves will be used to analyze the time until WOMAC improvement is first observed (i.e. time to improvement). The Turnbull method will be used to estimate these curves while accounting for interval censoring (the clinical improvement event is only known to have occurred between the current and prior visit).

10. Records, Confidentiality and Data Monitoring
Each patient will be identified by a study ID number only in the trial records. Study data will be recorded on pre-printed case report forms (CRFs). Monitoring of study data recorded on source documents and reported on study CRFs will be conducted for all patients to ensure accuracy and completeness. All data will be stored on a HIPAA compliant online resource.

11. Quality Control and Assurance
Complete and accurate data collection and reporting will be the responsibility of the Principle Investigator.

12. Good Clinical Practice
This investigation will be conducted in accordance with the International Conference on Harmonization (ICH) E6 for Good Clinical Practice (GCP): Consolidated Guidance and all appropriate regulatory requirements. The Investigator will be thoroughly familiar with the appropriate use of the treatment procedure as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established by the site personnel at the beginning of the study, maintained for the duration of the trial and retained according to all appropriate regulations.

13. Ethical Considerations
The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB) will review all appropriate study documentation, including the protocol, informed consent and any advertisements that will be used for the study in order to safeguard the rights, safety and wellbeing of the patients. The study will only be conducted once IRB approval has been obtained. The Investigator will provide safety updates, annual progress reports and any revisions to these documents to the IRB as required by regulations.

14. Patient Information and Informed Consent
After the study has been fully explained to each patient in their preferred language, written informed consent (also in the patient's preferred language) will be obtained from each patient prior to any study-specific procedures being performed. The IRB will approve the informed consent form prior to use. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all other applicable regulatory requirements.

15. Patient Confidentiality
In order to maintain patient privacy, all case report forms (CRFs), study reports and communications will identify the patient by their assigned study ID only. The patient's confidentiality will be maintained and will not be made publically available to the extent permitted by the applicable laws and regulations.

16. Retention of Study Data
University of California Los Angeles (UCLA) Medical Center will retain the written and/or electronic medical records, reports and data relating to the study in a secure location for a period of ten (10) years. UCLA Medical Center will prepare and maintain accurate written records of and data from the study.

17. References

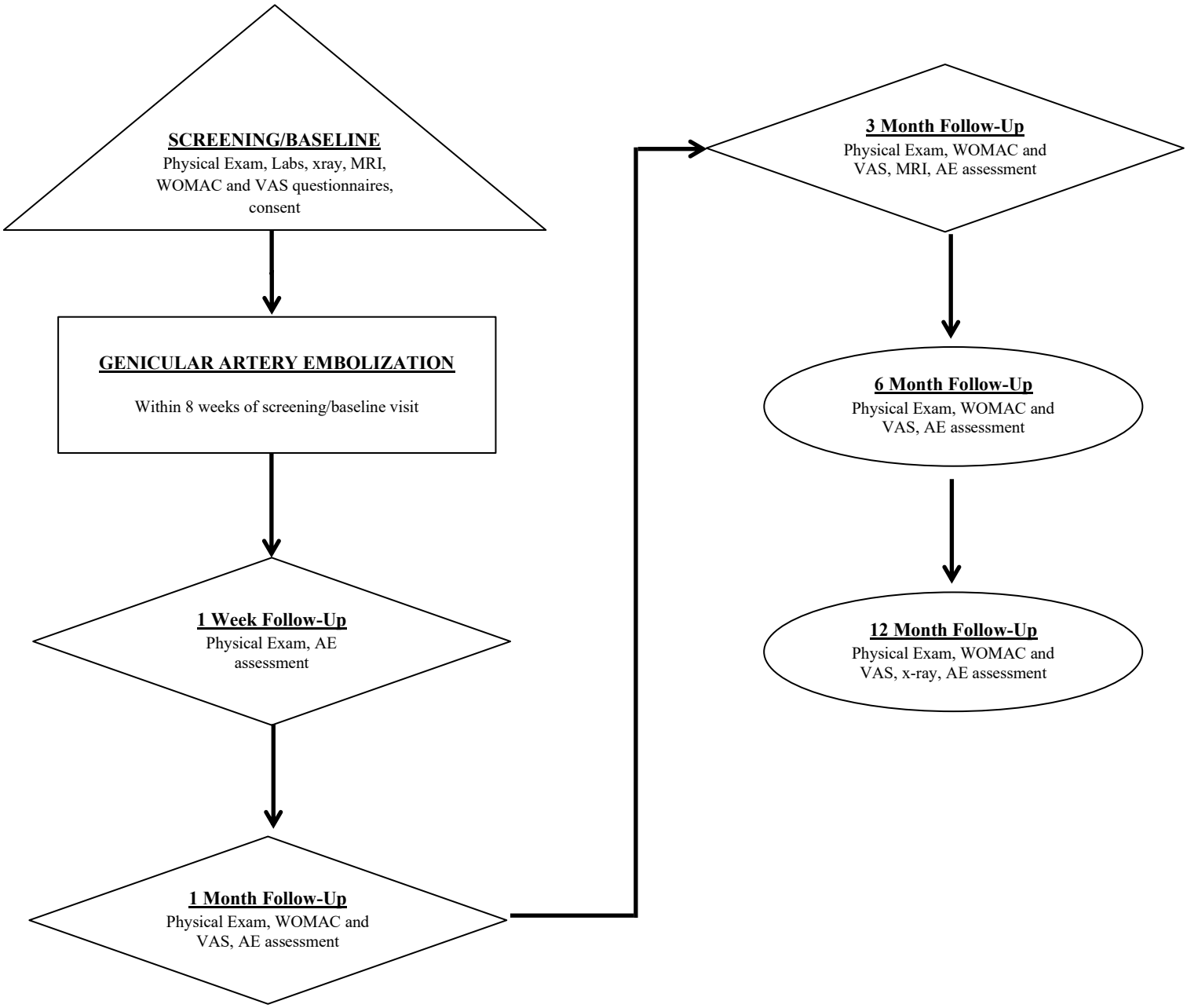
1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Ann Rheum Dis. 2014 Jul;73(7):1323-30. PubMed PMID: 24553908.
2. Dominick KL, Ahern FM, Gold CH, Heller DA. Health-related quality of life and health service use among older adults with osteoarthritis. Arthritis Rheum. 2004 Jun;51(3):326-31. PubMed PMID: 15188315.
3. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013 Jan;21(1):16-21. PubMed PMID: 23194896.
4. Pap T, Distler O. Linking angiogenesis to bone destruction in arthritis. Arthritis Rheum. 2005 May;52(5):1346-8. PubMed PMID: 15880805.
5. Ashraf S, Wibberley H, Mapp PI, Hill R, Wilson D, Walsh DA. Increased vascular penetration and nerve growth in the meniscus: a potential source of pain in osteoarthritis. Ann Rheum Dis. 2011 Mar;70(3):523-9. PubMed PMID: 21081524.
6. Okuno Y, Korchi AM, Shinjo T, Kato S, Kaneko T. Midterm Clinical Outcomes and MR Imaging Changes after Transcatheter Arterial Embolization as a Treatment for Mild to Moderate Radiographic Knee Osteoarthritis Resistant to Conservative Treatment. J Vasc Interv Radiol. 2017 Jul;28(7):995-1002. PubMed PMID: 28365171.
7. Okuno Y, Korchi AM, Shinjo T, Kato S. Transcatheter arterial embolization as a treatment for medial knee pain in patients with mild to moderate osteoarthritis. Cardiovasc Intervent Radiol. 2015 Apr;38(2):336-43. PubMed PMID: 24993956.
8. Gbolahan OB, Schacht MA, Beckley EW, LaRoche TP, O'Neil BH, Pyko M. Locoregional and systemic therapy for hepatocellular carcinoma. J Gastrointest Oncol. 2017 Apr;8(2):215-28. PubMed PMID: 28480062.
9. Stampfl U, Radeleff B, Sommer C, Stampfl S, Dahlke A, Bellemann N, et al. Midterm results of uterine artery embolization using narrow-size calibrated embozene microspheres. Cardiovasc Intervent Radiol. 2011 Apr;34(2):295-305. PubMed PMID: 20953610.
10. Gynecologists ACoOa. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol. 2008 Aug;112(2 Pt 1):387-400. PubMed PMID: 18669742.
11. Weidner ZD, Hamilton WG, Smirniotopoulos J, Bagla S. Recurrent Hemarthrosis Following Knee Arthroplasty Treated with Arterial Embolization. J Arthroplasty. 2015 Nov;30(11):2004-7. PubMed PMID: 26092252.
12. Waldenberger P, Chemelli A, Hennerbichler A, Wick M, Freund MC, Jaschke W, et al. Transarterial embolization for the management of hemarthrosis of the knee. Eur J Radiol. 2012 Oct;81(10):2737-40. PubMed PMID: 22154590.
13. Bonomo G, Pedicini V, Monfardini L, Della Vigna P, Poretti D, Orgera G, et al. Bland embolization in patients with unresectable hepatocellular carcinoma using precise, tightly size-calibrated, anti-inflammatory microparticles: first clinical experience and one-year follow-up. Cardiovasc Intervent Radiol. 2010 Jun;33(3):552-9. PubMed PMID: 19957182.
14. Greco G, Cascella T, Facciorusso A, Nani R, Lanocita R, Morosi C, et al. Transarterial chemoembolization using 40 μm drug eluting beads for hepatocellular carcinoma. World J Radiol. 2017 May;9(5):245-52. PubMed PMID: 28634515. PMCID: PMC5441456.
15. Hlavica M, Ineichen BV, Fathi AR, Remonda L, Diepers M. Parasagittal Dural Arteriovenous Fistula Treated With Embozene Microspheres. J Endovasc Ther. 2015 Dec;22(6):952-5. PubMed PMID: 26337189.

Appendix A: Schedule of Study Events

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screening (within 8 weeks of Day 1)	Treatment (Day 1)	Week 1 (day 4-10)	Month 1 (4 weeks ± 2 weeks)	Month 3 (12 weeks ± 2 weeks)	Month 6 (24 weeks ±2 weeks)	Month 12 (52 weeks ± 2 weeks)
Informed Consent	X						
Eligibility criteria assessment	X						
Demographics	X						
Medical History	X						
Concurrent Medical Conditions	X						
Physical Examination	X		X	X	X	X	X
Vital Signs	X		X	X	X	X	X
Laboratory Evaluations[1]	X						
WOMAC	X			X	X	X	X
VAS	X			X	X	X	X
PRO and PGIC							X
Knee x-ray[2]	X						X
Knee MRI[3]	X				X		
GAE		X					
Adverse Events		X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X
Protocol violations	X	X	X	X	X	X	X

[1] Laboratory evaluations include complete blood count and serum chemistry
[2] Screening knee X-Ray can be performed within 6 months before Visit 1.
[3] Screening knee MRI can be performed within 6 months before Visit 1. If patients cannot undergo MRI (e.g. pacemaker, significant claustrophobia), then CT of the knee without contrast will be performed.

Appendix B: Study Flow Chart



Appendix C: Technical Protocol for Genicular Artery Embolization

- Immediately prior to the procedure, appropriate knee will be marked. Discern areas of focal point tenderness (up to 3 locations) and place radio-opaque BB marker.
- Administer prophylactic IV antibiotics, based on institution standard of care. Choice of antibiotic and sedation will be at the discretion of the interventional radiologist.
- Local anesthesia should be administered for a transfemoral approach on the side with the best arterial pulse, preferably on the same side as the affected knee.
- Access of the common femoral artery with a 21-gauge needle, with exchange to a 3-5 French sheath
- Angiogram of the superficial femoral artery (thigh)
- Catheterization of the distal superficial femoral artery, with repeat angiogram.
- Intraprocedural rotational c-arm CT of the knee with concurrent contrast injection in the distal superficial femoral artery
- Selective catheterization of the specific genicular arteries that are supplying the areas of the patient's pain, with repeat angiogram.
- If hypervascularity is seen, embolization is performed with 100 micron Embozene particles, suspended in a diluted solution of contrast and saline.
- Procedural endpoint is lack of distal hypervascularity, with preservation of normal arterial flow. Arterial stasis should not be achieved.
- Perform follow up angiography after each vessel is embolized to evaluate genicular devascularization and to identify any remaining collateral blood supply to the knee.
- Once the embolization procedure is complete, follow institution's standard of care for catheter and introducer removal and closure of femoral puncture. This will typically be done with manual compression.
- It is suggested that patients be discharged with and oral non-opioid analgesic, 4-6 hours after the procedure.

Appendix D: Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC, version 3.1)

Instructions: Please rate the activities in each category according to the following

scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

Circle one number for each activity

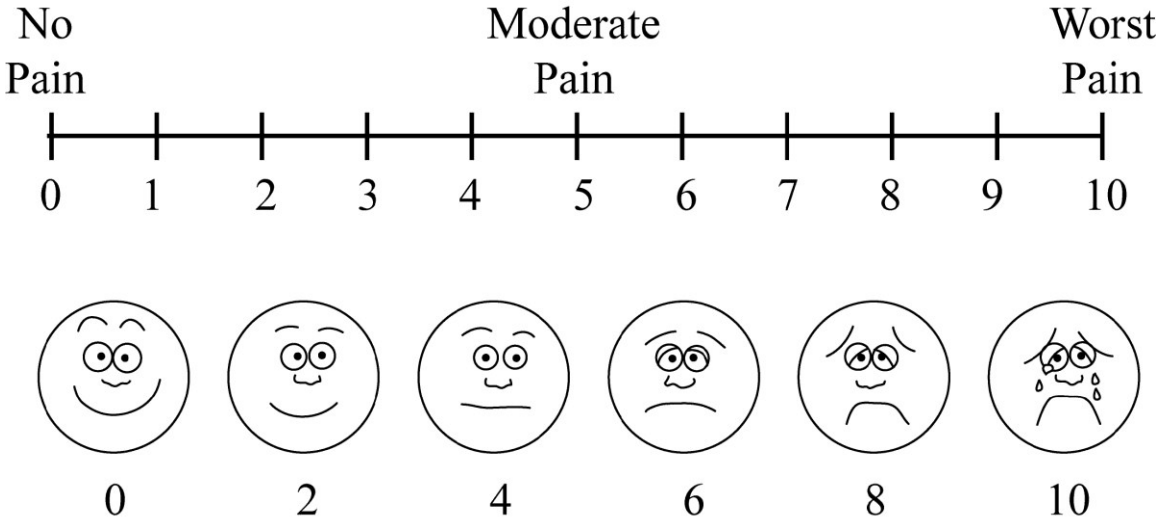
Pain	1. Walking	0	1	2	3	4
	2. Stair Climbing	0	1	2	3	4
	3. Nocturnal	0	1	2	3	4
	4. Rest	0	1	2	3	4
	5. Weight bearing	0	1	2	3	4
Stiffness	1. Morning stiffness	0	1	2	3	4
	2. Stiffness occurring later in the day	0	1	2	3	4
Physical Function	1. Descending stairs	0	1	2	3	4
	2. Ascending stairs	0	1	2	3	4
	3. Rising from sitting	0	1	2	3	4
	4. Standing	0	1	2	3	4
	5. Bending to floor	0	1	2	3	4
	6. Walking on flat surface	0	1	2	3	4
	7. Getting in / out of car	0	1	2	3	4
	8. Going shopping	0	1	2	3	4
	9. Putting on socks	0	1	2	3	4
	10. Lying in bed	0	1	2	3	4
	11. Taking off socks	0	1	2	3	4
	12. Rising from bed	0	1	2	3	4
	13. Getting in/out of bath	0	1	2	3	4

	14. Sitting	0	1	2	3	4
	15. Getting on/off toilet	0	1	2	3	4
	16. Heavy domestic duties	0	1	2	3	4
	17. Light domestic duties	0	1	2	3	4

Pain Score (1-5): _____

Total Score: _____

Appendix E: Visual analog pain score



Appendix F: Embozene Instructions For Use (IFU)

See attached document.

Appendix G: PRO and PGIC Questionnaire

1. Since the procedure, how would you describe the change (if any) in activity limitations, symptoms, emotions, and overall quality of life related to your knee arthritis?

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

2. If you could go back in time, knowing what you know now - would you have the procedure done again?

1. Yes
2. No