Randomized Placebo-Controlled Single Blinded Study of Geniculate Artery Embolization for Knee Pain Secondary to Osteoarthritis

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Protocol Title:	**Randomized Placebo-Controlled Single Blinded Study of Geniculate Artery Embolization for Knee Pain Secondary to Osteoarthritis**
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Medical Device:	Gel-Bead embolization spheres; OptiSphere embolization spheres
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1 Introduction

1.1 Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

1.2 Background

Osteoarthritis (OA) is a common and major cause of pain and disability. An estimated 26.9 million adults in the US suffer from OA[1] and nearly 50% of adults may develop symptomatic knee OA by age 85[2]. Knee OA affects obese individuals at a higher rate with ⅔ of individuals developing symptomatic disease. The treatment for knee osteoarthritis is broad and includes: exercise and patient education; pharmacologic therapies, including oral, topical, and intra-articular medications; and surgical interventions, including total joint arthroplasty. Minor symptoms can be managed with non-opioid pain medications such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), which are the mainstay of pain management for OA. Severe and end-stage osteoarthritis can be treated with total joint arthroplasty. Unfortunately, NSAIDs can be a cause of renal failure, exacerbation of asthma and most notably, gastrointestinal hemorrhage. Number of deaths from NSAID-related gastrointestinal bleeding has been estimated at 16500[3]. With the significant morbidity associated with treatment of OA, there is a need to develop a new, effective, minimally invasive and safe treatment for pain related to osteoarthritis of the knee.

The principal symptom of OA pain is mediated by a number of factors. However, angiogenesis resulting in neovascularity, neural sensitization and inflammation has been described as a potential pathophysiological pathway of the deep joint pain described by many OA patients[4, 5]. This increased vascularity in the setting of pain and OA has been the focus of recent endovascular investigation, with the proposed mechanism of embolization as a novel treatment.

Particulate embolization of geniculate artery branches supplying hypervascular joint tissue, the same technique we are proposing to treat pain from OA, has been previously described as a safe treatment for hemorrhage after total knee arthroplasty in multiple reports [6, 7,8, 9]. In 2008, three cases were reported using 150-355 micrometer particles without any complications[6]. In 2013, a Japanese group reported the use of 1000-2000 micrometer particles in the treatment of five patients, again without complication[9]. In 2015, an author group that includes one of the Co- PIs reported outcomes from 13 cases in which there were no major complications and two minor complications (transient cutaneous ischemia)[8]. Finally, in 2016 a fourth report of 14 embolizations was published in

which there were no major complications and, again, two minor complications (transient cutaneous ischemia)[7].

Embolization of hypervascular joint tissue for the treatment of pain has been pioneered by Dr. Okuno and his colleagues, in Japan. They initially reported a case series in which they were able to reduce pain related to refractory tendinopathy and enthesopathy in multiple joints in 7 patients using an antibiotic particulate for embolization without major complication[10]. Subsequently, the same team published its experience with transcatheter embolization of hypervascular tissue within the shoulder joint in 7 patients diagnosed with adhesive capsulitis. The procedure successfully resulted in pain reduction without any complications[11]. Finally, Okuno et al also published their results after synovial embolization in patients with painful OA. The procedure was performed on 14 patients and there were no major complications. There was significant pain reduction and decreased difficulty of movement at 4 months. Medication frequency also decreased after embolization[12]. Most recently, the same group published a larger cohort[13] of 72 patients with follow-up with midterm follow-up. Geniculate artery embolization was technically successful in in all patients. It was clinically successful in 86.3% of patients at 6 months and 79.8% at 3 years. MRI follow-up in patients demonstrated no osteonecrosis or other evidence of progression of degenerative changes.

The current investigation team has led efforts pioneering embolization procedures in novel targets that have proved successful[14,15,16,17,18,19]. We have also had experience in embolization of the knee, in particular with post-arthroplasty hemorrhage[8]. The principal investigator/sponsor is also an Investigator on a pilot study of GAE for knee pain, with a current Investigational Device Exemption (IDE) at UNC Chapel Hill. With our proven experience in embolization, and in particular the local-regional anatomy, we have set forth to pursue a US study evaluating embolization as a treatment for OA related knee pain versus placebo to demonstrate the actual effect of embolization on pain and disability.

1.3 Medical Device

1.3.1 Name of Investigational Device

Gel-Bead embolization spheres; OptiSphere embolization spheres

1.3.2 Intended Use of the Investigational Device

Gel-Bead embolization spheres; OptiSphere embolization spheres will be used for geniculate artery embolization (GAE) in subjects with knee osteoarthritis.

1.3.3 Description of the Investigational Device

Gel-Bead embolization spheres; OptiSphere embolization spheres were found to be substantially equivalent and cleared medical devices (Premarket Notification K133237) to prior technologies:

- Emboshpere Microshperes (Biosphere Medical, Inc/Merit Medical Systems, Inc, K021397), and

- Gel-Block Embolization Pledgets (Vascular Solutions, Inc, K113266)

Identified in the Code of Federal Regulations 21 Part 870- Subpart D-Cardiovascular Prosthetic Devices.

Classification Name: Artificial Embolization Device. Class II Medical Device
Common Name: Vascular Embolization Device Subpart D-Prosthetic Devices; Sec. 870.3300

Indication for Use: Gel-Bead embolization spheres; OptiSphere embolization spheres is intended for use in embolization of hypervascular tumors.

The Gel-Bead embolization spheres; OptiSphere embolization spheres (Gel-Bead) consists of biodegradable gelatin spheres pre-filled in a 20ml syringe. The syringe contains 1 ml of spheres suspended in 5 ml of saline. Gel-Bead is offered in four size ranges: 100-300 um, 300-500 um, 500-700 um and 700-1000 um. The spheres are intended to be used with a delivery catheter with an inner diameter that is adequate for sphere delivery (not included). The finished product is sterilized by Gamma irradiation and is intended for single use only. They come in a liquid suspension that is mixed with iodinated contrast before use. Once a catheter has been fluoroscopically guided into the target vessel, the embolization spheres are then injected, causing obstruction at the arteriole level until the desired degree of embolization has occurred. The embolization spheres used during the study will be unchanged.

1.4 Preclinical Data

Gel-Bead embolization spheres; OptiSphere embolization spheres have proven to be an effective embolization material with high biocompatibility in non-human studies. A GLP animal study was conducted on twelve mature miniature swine, with animals survived up to 12 weeks following implantation[20]. Eight animals were implanted with Gel-Bead and four animals implanted with a control (Embosphere). Gel-Bead spheres were consistently and reliably implanted in the selected target arteries of appropriate size and not in additional non-target tissues or regions. All instances of Gel-Bead delivery resulted in successful arterial occlusion at the time of implant, as confirmed by angiography. There were similar well-demarcated foci of infarction, indicative of successful embolization, observed in the target organs of both test article and control article animals. There were no clinically significant abnormalities identified in the clinical pathology blood results that negatively reflected on either the test or control devices. Examination of the tissues distant to the implantation sites did not identify any systemic abnormalities. Verification, animal study, and biocompatibility test results met the specified acceptance criteria and did not raise new safety or performance issues. Therefore, Gel-Bead is substantially equivalent to the predicate devices.

1.5 Clinical Data to Date

Gel-Bead embolization spheres; OptiSphere embolization spheres is substantially equivalent to predicate microsphere devices such as Embosphere. Embosphere

has have been safely used as an embolic agent to target hypervascular lesions throughout the body including uterine fibroids [21], benign prostatic hyperplasia[22], meningioma[23], and adenomyosis[24]. The investigators have also performed GAE for knee hemarthrosis with technical and clinical success using Embosphere microspheres[8]. Recently, embolization spheres have been used safely and effectively for GAE to treat knee pain in the setting of osteoarthritis[12]. Gel-Bead embolization spheres; OptiSphere embolization spheres are FDA approved for the treatment of arteriovenous malformations and hypervascular tumors.

2.0 Study Objectives

The primary aim of this study is to determine if GAE will reduce the severity of pain as well as global disability (resulting from the combination of pain, stiffness and difficulty performing daily activities) caused by knee OA compared with placebo. The secondary aim is to determine if GAE can result in the decreased necessity for ongoing conservative OA therapies such as medication therapy and joint injections.

3 Study Design

3.1 General Design

This will be a single-blinded randomized-controlled study of GAE versus placebo in a small population with knee pain secondary to arthritis to determine safety and efficacy. After IRB approval of a written informed consent and over, approximately a 24 month duration, N=21 subjects will be recruited. Only subjects ≥ 40 years will be screened for study recruitment. Subjects will be randomized in a 2:1 ratio of GAE:Placebo and will be blinded from study treatment (see flow chart below). The placebo procedure will be a diagnostic angiogram of the knee, without embolization. Appropriate measures will be taken to ensure patients and nursing staff caring for the patient are blinded to assignment. Each patient will be told at the time of recruitment that they may be randomly assigned to sham, but if after 1 month they have not had symptom improvement, their assigned procedure would be revealed and, if they had undergone a sham procedure, they will be allowed to proceed with embolization. This second procedure should be shorter than a complete angiogram and embolization, as the detailed angiogram will not need to be repeated, and therefore both arms will have similar total radiation dose.

Clinical procedures and evaluations will consist of a preoperative screening assessment to determine if the potential study subject meets the inclusion and exclusion criteria, enrollment, surgical procedure for geniculate artery embolization, and follow-up visits at 24 hours, 2 weeks, 1, 3, 6, & 12 months. An MRI will be performed after the 1-month visit in those patients who underwent embolization to detect a change in synovial vascularity and to exclude complication.

3.2 Primary Study Endpoints

1. Overall efficacy of treatment as determined by a minimal clinically significant reduction in global Western Ontario and McMaster University

Osteoarthritis Index (WOMAC) questionnaire scoring of 16% at 1 and 6 month follow-up.
2. Minimal clinically important decrease of 15% on the pain VAS at 1 or 6 months follow-up.

3.3 Secondary Study Endpoints

1. Reduction of previously initiated OA medical therapy (e.g. NSAIDs) at 12 months follow-up.

3.4 Primary Safety Endpoints

1. GAE without major complication.

4 Subject Selection and Withdrawal

4.1 General Characteristics of the Proposed Subject Population

Study subjects will be men and women with knee osteoarthritis resulting in knee pain that is refractory to conservative therapies, who are not planning to undergo surgery within 12 months.

4.2 Anticipated Number of Research Subjects

Enrollment into the investigation will be defined as providing informed consent for study participation per IRB policies.

Twenty-one (21) subjects will be enrolled and all are anticipated to complete the study.

4.3 Inclusion Criteria

1. Moderate to severe knee pain (VAS > 50 mm), and
2. Pain refractory to at least 3 months* of conservative therapies (anti-inflammatory drugs, or physical therapy, or muscle strengthening, or intra-articular injections), and
3. Kellgren-Lawrence grade 1, 2 or 3 on radiograph of the knee.
4. Age > 40 years.

*3 months was chosen because this time interval is thought adequate for knee pain to be considered refractory to conservative care.

4.4 Exclusion Criteria

1. Current local infection, or
2. Life expectancy less than 6 months, or
3. Known advanced atherosclerosis, or
4. Rheumatoid or infectious arthritis, or
5. Prior knee replacement surgery, or
6. Uncorrectable coagulopathy including INR > 2.5 or platelets < 30,000, or
7. Iodine allergy resulting in anaphylaxis, or
8. Renal dysfunction as defined by serum creatinine >1.6 dl/mg or eGFR <60 obtained within the past 30 days.

4.5 Subject Recruitment and Screening

Subjects will be recruited from orthopedic and interventional radiology clinics in

the Northern Virginia Area or the Vascular Interventional Radiology Clinic at UNC-Chapel Hill.

4.6 Early Withdrawal of Subjects

4.7.1 Criteria for Removal from Study

Subjects will be withdrawn from the study if

a. a major complication occurs that prevents completion of GAE or the ability to complete the follow up visits, or
b. at any point at their discretion.

4.7.2 Follow-up for Withdrawn Subjects

If a subject withdraws from the study, any recorded data will still be included in the analysis. Subjects will only be replaced if they withdrew prior to undergoing GAE.

5 Study Treatment or Diagnostic Product Procedures

5.1 Description

Subjects will not initiate any new pain therapy or escalate current therapy for 1 month prior to GAE. They will be given an intravenous dose of antibiotics on the day of the procedure and continue with oral antibiotics for seven days after the procedure. The subjects will be given the choice of receiving intravenous anxiolytic and analgesic medication during procedure or proceeding with local anesthetic only.

Arterial access site will be prepped and draped using sterile technique. Ultrasound-guided access may be used and arterial access will be obtained. An intra-arterial sheath will be placed. Through this sheath a guiding catheter will be used to perform lower extremity angiography on the targeted side. Using the guiding catheter and a microcatheter, the geniculate arteries supplying hypervascular synovial tissue in the region of the knee joint will be catheterized. This will allow the operators to know exactly what tissues will be receiving the Gel-Bead embolization spheres; OptiSphere embolization spheres. Gel-Bead embolization spheres; OptiSphere embolization spheres ranging from 100-500 microns*, selected at the operator's discretion based upon size of target vessels, will then be injected under fluoroscopic guidance to prevent reflux and non-target embolization. Injection will continue until an end point of at least 'near stasis' (slowed antegrade flow of contrast). Multiple geniculate arteries may be embolized until neovascularity is no longer seen. A repeat lower extremity angiogram will then be performed to evaluate for success of embolization and to exclude complication. The catheter and sheath will then be removed and hemostasis will be achieved with manual compression or a vascular closure device. The subject subsequently will be discharged home the same day (<23hours) unless a complication arises that requires inpatient admission for management of the complication. Subjects may be discharged on pain medications as needed for post-operative care (<14 days).

**The range in size of particles will allow the operators to discern the safest, most effective size for the vessels targeted. For example, if the catheter can be*

*advanced all the way in to the branch supplying only the synovium, smaller particles can be safely used to induce ischemia in the target tissue. If the catheter cannot be advanced due to tortuous or small caliber vessels, a larger sized particle may be selected. This will allow for proximal embolization without distal penetration into the cutaneous branches, thereby allowing continued blood flow to the skin through collateral pathways (**Fig 1-2**). This concept is utilized routinely within embolization procedures are commonly performed.*

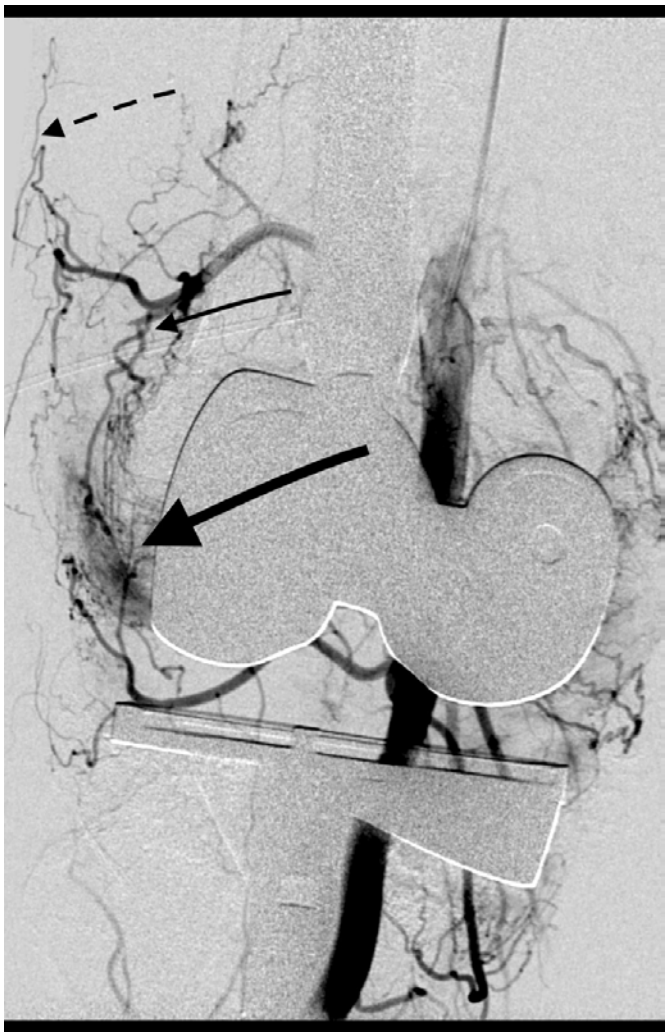


Fig 1. Geniculate artery angiogram after total knee arthroplasty demonstrating "contrast blush" denoting hypervascular synovium (bold arrow). Separate arterial branches are seen supplying the joint tissue (arrow) and skin (dotted arrow). At this point an attempt would be made to place a microcatheter in the synovial branch. If impossible due to the size of the target vessel, embolization would be performed from this catheter location using larger particles to preserve distal collateral supply to the skin.

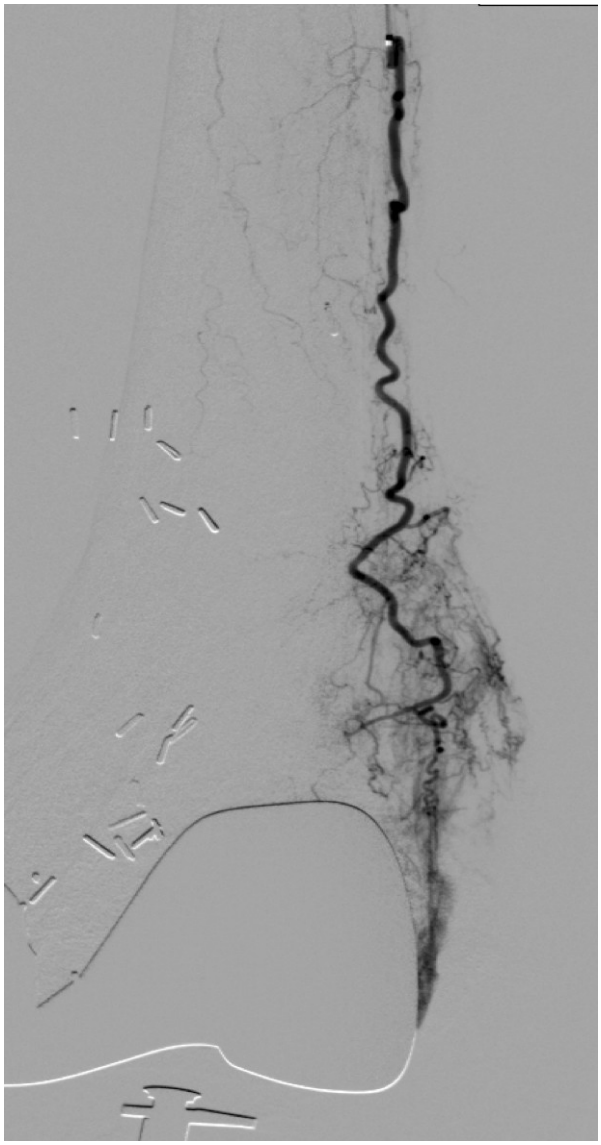


Fig 2. Lateral angiogram of the knee with selective catheterization of the synovial branch of the geniculate artery. In this circumstance, smaller sized embolic particles would be appropriate because cutaneous branches are not seen.

It is anticipated that less than 5 milliliters of Gel-Bead embolization spheres; OptiSphere embolization spheres will be required for embolization. Gel-Bead embolization spheres; OptiSphere embolization spheres currently have FDA approval for embolization of hypervascular tumors.

5.2 Method for Assigning Subject to Treatment Groups

Subjects who meet all criteria for study entry and have signed written informed consent will be randomized in a 2:1 allocation of treatment (geniculate artery embolization) versus placebo (angiogram). Patients will be blinded to the study procedure. Each patient will be told at the time of recruitment that they may be

randomly assigned to GAE or sham. If after 1 month if they have not had symptom improvement, their assigned procedure would be revealed only if they had undergone a sham procedure. They will then be allowed to proceed with embolization in Arm C if they elect to proceed. This second procedure should be shorter than a complete angiogram and embolization, as the detailed angiogram will not need to be repeated. See table 1 (study schema). A 2:1 ratio was selected so that patients would be more likely to enroll in the study.

5.3 Subject Compliance Monitoring

Study coordinators and physicians will inquire of the subjects to determine if they have escalated any current or initiated any new conservative therapies during the follow-up period.

5.4 Prior and Concomitant Therapy

The subjects will be required to have been on conservative therapy for OA for at least three months prior to undergoing GAE. They will be allowed to continue previously initiated therapies throughout the study period, but if new or escalated therapies are required past the post-operative period (14 days), the treatment will be considered a failure.

5.5 Blinding of Study

Following randomization, efforts will be made to blind the subject to the study procedure. Patients will not be informed to their treatment or placebo arm. As the procedures of a diagnostic angiogram and embolization are similar (femoral artery access, angiogram, post-operative care), the subject will inherently not know if he/she received the treatment or placebo. The post-operative staff caring for the patient will not be informed as to the treatment the patient received. Datasets for each arm will be presented for analysis by statistician labeled as treatment arm (i.e. A, B or C).

5.6 Receiving, Storage, Dispensing and Return

5.6.1 Receipt of Investigational Device Supplies

Medtronic will provide, at no charge, up to six (6) boxes (5 vials/box) of Gel-Bead Microspheres for the Study ("Devices"). Gel-Bead embolization spheres; OptiSphere embolization spheres will be stored within the Interventional Radiology Department in a separate area. Embolic devices will be labeled 'for investigational use only' and will be reserved for use in the clinical trial.

5.6.2 Storage

Gel-Bead embolization spheres; OptiSphere embolization spheres must be stored in a cool, dark, dry place in their original packing.

5.6.3 Dispensing

No study specific dispensing techniques will be used.

5.6.4 Return or Destruction of Investigational Device

The Institution and Sponsor-Investigator shall, return any such Product to

Company promptly if requested by the Company upon the completion or termination of the Study for which such Product was being utilized, or promptly dispose of or destroy, as the Company may reasonably direct, all of its remaining stocks of Product. All Devices supplied by Medtronic to Institution for the Study shall be used by Institution only as specified in the Protocol and the Clinical Trial Agreement. No other use of the Devices is authorized.

Disposable syringes, which spherical particulate is stored in, will be discarded as medical waste and packaging will be kept in a secure location until the study is completed. Packages will be disposed of upon completion of the study.

Lot numbers of the device used will be recorded in the CRFs for the study procedure.

6 Study Procedures

6.1 Screening Visit (Visit 1)

Potential enrollees will first be identified and will undergo a standard knee OA work-up to include history and physical exam with emphasis on specific site of knee tenderness. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire will be administered to assess difficulty as a result of pain, stiffness and overall decreased function secondary to knee pain in the past week.

Current pain will also be assessed using a visual analog scale (VAS). A knee radiograph will be obtained and evaluated using the Kellgren-Lawrence grading scale. A baseline knee MRI will also be acquired to evaluate for concomitant pathology as part of routine orthopedic evaluation. If the patient previously had an MRI for clinical care that can be obtained from his/her medical record and used for the purposes of this study.

If a patient qualifies to be a subject in the study based on the inclusion and exclusion criteria listed in section 4.3 and 4.4, the local study coordinator, investigator or designee will provide the candidate with a copy of the approved informed consent. Written informed consent will be obtained if appropriate. If the patient wishes to take more time to review the study before enrolling, he/she may complete the consent process at the beginning of the next visit, prior to the study GAE procedure. Those candidates who are disqualified from study entry will be logged into the Screening Log with a reason for no study entry. A copy of the consent will be provided to the subject and the original filed in the study files.

Patients will be randomized at this point according to the schema created prior to the commencement of the study.

6.2 Visit 2 GAE or Sham Procedure

GAE or sham procedure will be performed as described in part 5.1 above within 4 weeks of Visit 1. Subjects will be given a pager number to reach a physician (24 hours a day) to report any adverse symptoms and receive medical advice. The

sham procedure patients will be provided with the same information and follow-up instructions.

If a patient does not undergo the procedure within the specified visit window, then the WOMAC and VAS questionnaires should be repeated prior to the procedure.

6.3 Visit 3 -1 Day Follow-up

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, the day following GAE or sham procedure (+3 days). As most complications of the procedure will be evident within this time period, this visit is to evaluate for early AE's. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.4 Visit 4 – 2 Week Follow-Up

Patients will be called after 2 weeks to assess any adverse events, such as persistent pain.

6.5 Visit 5a and 5b - 1 Month Follow-Up

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, 30 +/- 7 days following GAE or sham procedure. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. An MRI of the treated knee will be acquired for those subjects who underwent GAE*. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies.

For those subjects who do not report improvement in symptoms or worsening, and are in the placebo arm, they will be unblinded and offered to undergo the geniculate artery embolization (Arm C) and then followed at similar follow-up intervals to 12 months (24 hours, 2 weeks, 1 month, 3 months, 6 months, and 12 months).

**MRI is only scheduled at one month in order to evaluate for non-target ischemic injury. These types of injuries will become apparent as early as 24 hours after embolization. Infarcted tissue will still be detectable at one month. Based on our experience with embolization in other areas, it is thought extremely unlikely that new ischemic injury related to the procedure will develop after the one-month follow-up. Additionally, findings that would be detected on later scans may be unrelated to the procedure and confound the data.*

6.6 Visit 6a and 6b - 3 Month Follow-Up for blinded subjects

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, 90 +/- 10 days following GAE or sham procedure. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies. If an AE is suspected based on change in pain scores or functionality, an appropriate

work-up will be performed which may include MRI.

6.7 Visit 6c - GAE for unblinded subjects

GAE will be performed (as described in part 5.2 above) within 4 weeks of visit 4. Subjects will be given a pager number to reach a physician, 24 hours a day, to report any adverse symptoms and receive medical advice.

6.8 Visit 7a and 7b - 6 Month Follow-Up for blinded subjects

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, 180 +/- 10 days following GAE or sham procedure. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.9 Visit 7c - 1 day follow-up for unblinded subjects

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, the day following GAE (+3 days). As most complications of the procedure will be evident within this time period, this visit is to evaluate for early AE's. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.10 Visit 8c – 2 Week Follow-Up for unblinded subjects (arm C only)

Patients will be called after 2 weeks to assess any adverse events, such as persistent pain.

6.11 Visit 9c-1 month follow-up for unblinded subjects

Subjects will be seen in clinic 30 +/- 7 days following GAE. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. An MRI of the treated knee will be acquired. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies.

6.12 Visit 10c- 3 month follow-up for unblinded subjects

Subjects will be seen in clinic or contacted by phone or by teleconference, per the subject's preference, 90 +/- 10 days following GAE. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.13 Visit 11c - 6 month follow-up for unblinded subjects

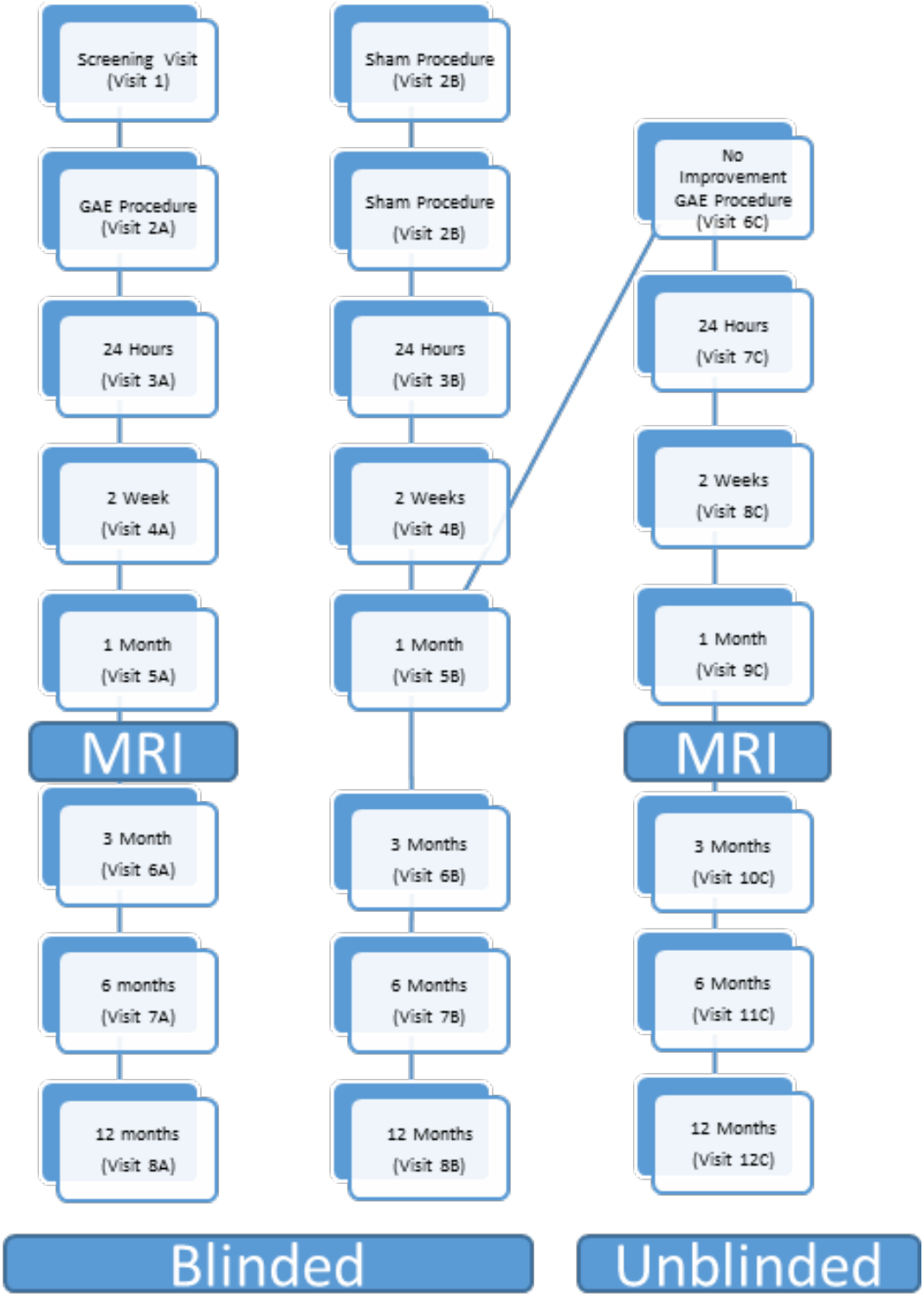
Subjects will be seen in clinic or contacted by phone or by teleconference per, the subject's preference, 180 +/- 10 days following GAE. The WOMAC

questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.14 Visit 8a, 8b, or 12c– 12 month follow-up for all subjects

Subjects will be seen in clinic or contacted by phone or by teleconference per, the subject's preference, 180 +/- 10 days following GAE. The WOMAC questionnaire and VAS pain score will be completed and subjects will be evaluated for possible adverse events. Subjects will also provide an update about the necessity/frequency of pre-established conservative therapies. If an AE is suspected based on change in pain scores or functionality, an appropriate work-up will be performed which may include MRI.

6.15 Study Procedure Flow Chart



7 Safety and Effectiveness Assessments

7.1 Safety Assessments

Subjects will be observed for several hours after GAE to monitor for immediate complications to include bleeding, infection and acute ischemia of the lower extremity. The subjects will be given a phone number that they can call to reach the principal investigator or designee if they believe they have developed a complication of the procedure. If at any point during the study period (including between scheduled follow-up visits) a subject reports symptoms that suggest an AE, an appropriate work-up will be initiated by the investigators to evaluate the etiology of the symptoms. This may include physical exam, laboratory tests and imaging (including MRI if appropriate).

7.2 Effectiveness Assessments

Technical success will be defined as devascularization of hypervascular synovium at the affected knee. This will be determined during the procedure. Clinical success will be defined as a 16% reduction of the baseline global WOMAC score at 1 or 6 month follow-up (primary outcome) and a 15% reduction of the baseline pain VAS score at 6 or 1 month follow-up (primary outcome).

8 Statistical Plan

8.1 Sample Size Determination

Using baseline WOMAC means and standard deviations of 12.2 and 1.9, respectively, from the Okuno study, we will have at least 69.1 % power to detect a clinically relevant difference of 16% for WOMAC for a one-sided alternative hypothesis. Actual power will be greater than this 69.1% lower bound since our analysis strategy uses data from multiple time points to formulate individual growth trajectories.

Using baseline VAS means and ranges of 72 and (54-100), respectively, we used the method of devised by S.P. Hozo, B. Djulbegovic, and I. Hozo to derive an estimate of the baseline standard deviation as 13.3. Given these parameters, we will have at least 51.7 % power to detect a clinically relevant difference of 15% for VAS for a one-sided alternative hypothesis. Actual power will be greater than this 51.7% lower bound since our analysis strategy uses data from multiple time points to formulate individual growth trajectories.

Power calculations used GPower, version 3.1.9.2.

8.2 Statistical Methods

The primary study endpoints, WOMAC and VAS scores, will be collected at baseline, 1 month follow-up, 3 month follow-up, and 6 month follow-up. Mean WOMAC and VAS scores will be reported at baseline, 1 month follow-up, 3 month follow-up, and 6 month follow-up, along with associated confidence intervals.

We will address the primary study endpoints by modeling each clinical outcome using random coefficient modeling. The clinical outcomes will be modeled as a linear function of time. We will allow a random intercept and slope that is dependent on treatment, so that each patient will have their own trajectory of pain over time. No additional covariates will be included in the model. We will employ a compound symmetric R-side covariance structure to account for dependencies arising from observations from the same patient. Random coefficient models are robust to missing values only require data to be MAR (and not the stronger assumption of MCAR), so that presence of missing values will not invalidate our conclusions.

We will compute predicted means, as well as the estimated difference in predicted means, at 6 months for both WOMAC and VAS; these will be derived from the population-averaged trajectories (i.e. fixed effects). We will test the H_0: $\mu_{\text{sham, 6 months}} - \mu_{\text{GAE, 6 months}} = 0$ versus the one-sided alternative hypothesis H_a: $\mu_{\text{sham, 6 months}} - \mu_{\text{GAE, 6 months}} > 0$ using a Wald test. Both primary study endpoints will be evaluated by considering significance of the p-value ($p < 0.05$) along with the percentage predicted mean difference with respect to the clinically relevant differences (16% for WOMAC and 15% for VAS). Both these factors will be taken in tandem as evidence to suggest GAE treatment efficacy. Primary endpoints will be assessed only at one time point, so that adjustment for multiple comparisons is not necessary since the evaluation of the primary endpoints for WOMAC and VAS each consists of only one statistical test.
Non-significance of the p-value for this test will be considered inconclusive evidence against the null hypothesis. Variance components, including the intraclass correlation coefficient, will also be reported for each model. All analyses will use SAS version 9.4 (SAS Institute, Inc., Cary, NC).

We will identify extreme primary endpoint values by computing studentized residuals and then conduct sensitivity analyses by deleting these outliers from the analysis datasets. We will repeat the above statistical tests and use results of the sensitivity analyses to corroborate conclusions reached in the primary analyses.

We will address the secondary study endpoint of reduction of OA by comparing frequency of OA medical therapy between the sham group, the crossover group, and the GAE group at 12 months. We will employ a chi-squared test to test the *H_0: frequency of OA medical therapy is equal for between the sham group, the crossover group, and the GAE group* versus the one-sided alternative hypothesis. A p-value of < 0.05 will be taken as evidence to suggest that the frequency of OA medical therapy is not equal between the groups. Non-significance of the p-value for this test will be considered inconclusive evidence against the null hypothesis.

Reduction in AE will be evaluated with a multilevel logistic regression model. The outcome of adverse events will be regressed on treatment status. We will employ a compound symmetric R-side covariance structure to account for dependencies arising from observations from the same patient. The *H_0: frequency of AE is equal for between the sham group and the GAE group* will be assessed versus the two-sided alternative hypothesis with a statistical test of the treatment

parameter different than 0, with a p-value of < 0.05 taken as evidence to suggest that the frequency of OA medical therapy is not equal between the groups. Non-significance of the p-value for this test will be considered inconclusive evidence against the null hypothesis.

8.3 Subject Population(s) for Analysis

A patient will be considered an evaluable study subject evaluable for data analysis per the following criteria, a written informed consent was obtained, he/she meets the inclusion and exclusion criteria, and received the GAE or sham study procedure. All subjects with 12 month follow-up data will be included for analysis even if some follow up data is incomplete. Every attempt will be made to ensure that there is as little missing data as possible including reminder phone calls and follow-up phone calls, if a subject misses a visit.

9 Risk Analysis

9.1 Anticipated Risks

Previous studies of lower extremity geniculate artery embolization for arthritis related pain have reported only one complication of moderate puncture site related hematoma (1/13), however this was a small population[12]. A recent study of GAE for recurrent hemarthrosis completed by one of the co-Is (Bagla) included 2/13 subjects who developed transient cutaneous ischemia that resolved within three weeks without intervention[8]. Additional risks that are anticipated but occur infrequently after any arterial intervention include infection, pain, pseudoaneurysm formation, arterial dissection and distal non-target embolization resulting in ischemia or necrosis. Detailed risk analysis is below:

	Risk or Side Effect	Source of Risk or Side Effect	Possible	Less Possible	Rare Events
Potential Risks Associated Study Enrollment & Study Procedures	Discomfort	Blood draw for lab test, ultrasound or MRI	X		
	Thrombophlebitis, bruising, bleeding, blood clot, Pre-syncope or Syncope (i.e. Fainting)	Blood draw for lab tests		X	
	Anxiety or Claustrophobia	MRI scan		X	
	Psychological Discomfort	Clinical Trial			X
	Infection	Blood draw for lab tests			X
	Allergic Reaction	MRI contrast			X

	Gadolinium contrast adverse reaction (i.e. Nephrogenic Systemic Fibrosis or severe skin reaction from contrast agent only reported in patients with kidney	MRI Contrast injection			X
	Confidentiality breach from Medical Records	Medical Record Keeping			X
	Groin/Anesthetic Injection/Neurologic Injury/	Pressure during arterial access	X		
	Discomfort/Pain	after catheter removed at the leg/femoral artery site	X		
Risks of the GAE Procedure and Post-operative care	Radiation Exposure Injury	GAE/Sham procedure			X
	Kidney Dysfunction	Contrast injected		X	
	Joint Infection	GAE Procedure		X	
	Adverse or Allergic Reaction	Intravenous contrast agent or medications administered as part of procedure or follow-up care		X	
	Tissue damage to Skin, Muscle, Skin or other structure in legs (Non-target Embolization)	GAE/Sham procedure			X
	Minor Bruising or Bleeding	GAE/Sham procedure			X
	Bleeding requiring Transfusion or surgery	GAE/Sham procedure			X
	Synovitis related symptoms including pain, stiffness or limited joint mobility	GAE procedure	X		
	Post Embolization Syndrome, including fever, malaise, headache, and myalgia (body aches)	GAE procedure		X	
	Internal bleeding, such as Gastrointestinal bleeding	Medications taken after the procedure (i.e. Ibuprofen)			X
	Infection	Catheter site in the leg/groin			X
	Arterial injury/trauma, laceration, bruising/pseudoaneury	Procedure/ Closure device (clip) on the			X
	Pulmonary embolism (clot in lung), Thrombophlebitis (clot in artery or vein)	GAE/Sham procedure and immobility			X

	Myocardial Infarction (Heart attack)	GAE/Sham procedure including moderate sedation/sedative			X
	Stroke	GAE/Sham procedure including moderate sedation/sedative			X
	Disability	GAE/Sham procedure including moderate sedation/sedative			X
	Death	GAE/Sham procedure including moderate sedation/sedative			X

9.2 Risk Minimization

The GAE procedure will be performed by board-certified interventional radiologists who have expertise in endovascular techniques, particularly in selective catheterization and transcatheter embolization techniques. Analgesia during the procedures will be provided through the use of conscious sedation if required. The risks of conscious sedation will be minimized by continuous monitoring of heart rate, blood pressure, oxygen saturation, and cardiac rhythm. The dose area product projected for the procedure is thought to be less than 30 gray/cm2 which is about 2-4 years of background radiation and significantly less than that of a cardiac catheterization. Radiation exposure will be minimized to subjects under the principal of 'as low as reasonably achievable' (ALARA).

Sterile instruments with a sterile technique will be used to minimize infection risk at the arterial access site. Pre-operative antibiotic(s) will be administered to reduce risk of other infections, such as urinary tract. The arterial access site discomfort will be minimized by administration of local anesthesia into the overlying skin and adjacent tissues. Catheter access into the appropriate artery may be performed using ultrasound-guided arterial puncture to prevent inadvertent vessel puncture with subsequent bleeding. Real-time fluoroscopic monitoring of all catheter/wire manipulations will be used to prevent vascular injury.

The subject will be monitored for the risk of an allergic response to iodinated contrast. To minimize the risk of renal dysfunction there will be use of non-ionic contrast agents, and appropriate pre-procedure hydration, when necessary. Subjects who report an allergic reaction to iodinated contrast will be pre-medicated as per routine allergy prophylaxis per standard of care.

9.3 Adverse Event Definitions

Adverse effect. Any untoward medical occurrence in a clinical study of an investigational device; regardless of the causal relationship of the problem with the device or, if applicable, other study treatment or diagnostic product(s).

Associated with the investigational device or, if applicable, other study treatment or diagnostic product(s). There is a reasonable possibility that the adverse effect may have been caused by the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Disability. A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse effect. Any adverse effect that places the subject, in the view of the investigator-sponsor, at immediate risk of death from the effect as it occurred (i.e., does not include an adverse effect that, had it actually occurred in a more severe form, might have caused death).

Serious adverse effect. Any adverse effect that results in any of the following outcomes: death, a life-threatening adverse effect, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

- *Hospitalization* shall include any initial admission (even if less than 24 hours) to a healthcare facility as a result of a precipitating clinical adverse effect; to include transfer within the hospital to an intensive care unit. Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse effect (e.g., for a preexisting condition not associated with a new adverse effect or with a worsening of the preexisting condition; admission for a protocol-specified procedure) is not, in itself, a serious adverse effect.

Unexpected adverse effect. Any adverse effect, the frequency, specificity or severity of which is not consistent with the risk information described in the clinical study protocol(s) or elsewhere in the current IDE application, as amended.

Unanticipated adverse device effect. Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.4 Recording of Adverse Events

Research subjects will be questioned about adverse effects in person or by telephone the day following the procedure. In addition, they will be given a pager number to reach a physician on call, 24 hours a day, to report adverse effects and receive medical advice. The subjects will also be questioned about possible adverse effects at each follow-up visit.

All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group, if applicable, or suspected causal relationship to the investigational device or, if applicable, other study

treatment or diagnostic product(s) will be recorded in the subjects' case histories. For all adverse effects, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the effect (i.e., whether the effect should be classified as a *serious adverse effect*) and; 2) an assessment of the causal relationship between the adverse effect and the investigational device or, if applicable, the other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or, if applicable, other study treatment or diagnostic product(s) will be followed until the effect (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator-sponsor.

An abnormal test finding will be classified as an *adverse effect* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
    - Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse effect.
- The test finding leads to a change in study protocol or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse effect by the Sponsor-Investigator.

9.5 Causality and severity assessment

The investigator-sponsor will promptly review documented adverse effects and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse effect; 2) if there is a reasonable possibility that the adverse effect was caused by the investigational device or, if applicable, other study treatment or diagnostic product(s); and 3) if the adverse effect meets the criteria for a *serious adverse effect*.

If the investigator-sponsor's final determination of causality is "unknown and of questionable relationship to the investigational device or, if applicable, other study treatment or diagnostic product(s)", the adverse effect will be classified as *associated with the use of the investigational device or study treatment or diagnostic drug product(s)* for reporting purposes. If the investigator-sponsor's final determination of causality is "unknown but not related to the investigational device or, if applicable, other study treatment or diagnostic product(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

9.6 Reporting of Adverse Effects and Unanticipated Problems

9.6.1 Reporting of adverse reactions to the FDA

The investigator-sponsor will submit a completed FDA Form 3500Ato the FDA's Center for Devices and Radiological Health for any observed or volunteered adverse effect that is determined to be an *unanticipated adverse device effect.* A copy of this completed form will be provided to all participating sub-investigators.

The completed FDA Form 3500Awill be submitted to the FDA as soon as possible and in no event, later than 10 working days after the investigator-sponsor first receives notice of the adverse effect.

If the results of the sponsor-investigator's follow-up evaluation show that an adverse effect that was initially determined to not constitute an *unanticipated adverse device effect* does, in fact, meet the requirements for reporting; the investigator-sponsor will submit a completed FDA Form 3500A as soon as possible, but in no event later than 10 working days, after the determination was made.

For each submitted FDA Form 3500A, the sponsor-investigator will identify all previously submitted reports that that addressed a similar adverse effect experience and will provide an analysis of the significance of newly reported adverse effect in light of the previous, similar report(s).

Subsequent to the initial submission of a completed FDA Form 3500A, the investigator-sponsor will submit additional information concerning the reported adverse effect as requested by the FDA.

9.6.2 Reporting Adverse Events to the Responsible IRB

In accordance with applicable policies of UNC-Chapel Hill and Vascular Institute of Virginia, the investigator will report, to the IRB, any observed or volunteered adverse effect that is determined to be (1) unexpected; (2) related or possibly related to the research; and (3) involves increased or greater risk of harm to participant(s) or others than was previously known or approved by the IRB. Adverse effect reports will be submitted to the IRB in accordance with the IRB policies and procedures.

9.7 Stopping Rules

The study will be stopped if there is greater than one major complication (Grade D, E or F) as defined by the Society of Interventional Radiology Classification System for Complications by Outcome (29).

9.8 Medical Monitoring

9.8.1 Data and Safety Monitoring Plan

Data and Safety Monitoring will be performed by a licensed physician who is not a study investigator.

Study Monitor will be:

Keith Smith, MD, PhD
UNC Department of Radiology
2016 Old Clinic Bldg
CB #7510
Chapel Hill, NC 275199-7510

The CRFs and any relevant source documents will be sent to the Study Monitor (as above) who will review them after treatment is complete for subjects 1, 5, 10 and 21.

Complications will be assessed by the co-PIs, categorized into major and minor categories and recorded on the CRF. CRFs and appropriate source documents will be made available to this individual for bi-monthly (every 2 months) review to ensure completeness of data collection. Any discrepancies will be immediately addressed by the co-PIs. All adverse events will be recorded and then summarized for inclusion in the final manuscript.

Data monitoring will be performed by Study Monitor listed above. CRFs and appropriate source documents will be made available to this individual for bi-monthly review to ensure completeness of data collection. Any discrepancies will be immediately addressed by the co-PIs.

9.8.2 Data and Safety Monitoring Board

Because this is a small study with only 21 subjects, no DSMB will be used for this study. Data and safety monitoring will be conducted by an individual (Study Monitor) who is not an investigator on this study (see above).

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Consistent with these regulations a signed authorization will be obtained that informs each subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical-technical departments involved in the clinical trial.

10.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Copies of completed CRFs with subject IDs will be scanned and sent to the lead study coordinator at UNC for verification through the study database. Data should be entered in the study database within 5 business days to ensure timely entry.

The coordinator at each site will complete the first CRF together with one of the Co-PIs to verify that it is completed correctly. Then, we will verify a randomly selected 25% of all source docs at the conclusion of data collection. Randomization will occur on a visit level and not per patient. The randomization for this verification will be generated using a random number generator in Excel. A concealed randomization look-up table will be generated in collaboration with the biostatistician and installed in the REDCap database. Assignments remain concealed to the staff until the moment the participant is enrolled online in the REDCap database.

10.4 Record Retention

It is the investigators' responsibility to retain study essential documents during the investigation and for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Research records and original signed consent forms are to be retained by principal investigator for at least 6 years if the form includes authorization for use of private health information. Investigators may need to retain these documents for a longer period if required by an agreement with a sponsor or per other applicable regulatory requirements. The 6 year minimum retention of authorizations complies with the privacy regulation requirements.

10.5 IRB Documentation

The co-principal investigators and research coordinator will be responsible for maintaining IRB correspondence. IRB approved forms maintained, as part of the study will include the subject consent form and the HIPAA authorization form.

11 Study Monitoring, Auditing and Inspecting

11.1 Study Monitoring Plan

11.1.1 Locations

Initial enrollment will occur at either an orthopedic clinic or in an interventional radiology clinic in the Northern Virginia area or at UNC-Chapel Hill. The procedures will be performed in Vascular Institute of Virginia Interventional Radiology or UNC-Chapel Hill procedural suites. Follow-up visits will occur at Vascular Institute of Virginia, UNC-Chapel Hill, or via phone or teleconference.

11.1.2 Study Staff Responsibilities and Training

CITI Training:
The investigators and all staff involved in the study will have completed their required CITI training in the protection of human research subjects and Good Clinical Practice training. Alternate training modules, as requested by local IRB, may also suffice.

Drs. Isaacson, Piechowiak, and Bagla (fellowship trained interventional radiologists with subspecialty board certification) will be the only primary operators for each of the GAE's. Drs. Isaacson, Piechowiak, and Bagla have performed more than 600 arterial embolization procedures.

Any of the investigators may conduct follow-up visits as determined by the subjects' and investigators' availability.

All subjects will be coded by an alphanumeric identifier (letters [initials] and site number) and subject identity will be kept confidential. Subjects will be apprised during the informed consent review that they have the right to voluntarily withdraw from the study at any time for any reason, and that his decision will not affect his medical care, but for attrition analysis subjects will be asked their reason for withdrawal .

11.1.3 Quality Assurance and Quality Control

The research coordinator will monitor the study files on a monthly basis to ensure the appropriate regulatory and IRB documentations are on file and up to date. The research coordinator will also be responsible for

ensuring proper study documentation in order to verify compliance with Institutional policy, IRB, FDA and GCP guidelines in the following areas: Informed consent, Protocol, Source Documents and Electronic Case Report Forms.

11.1.4 Safety Monitoring

The research coordinator will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or safety monitor of all Unanticipated Problems/SAE's.

The research coordinator and co-principal investigators will confirm that all Adverse effects (AE) are correctly entered into the AE log by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; notify the IRB and FDA of all Unanticipated Problems/SAEs and AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The research coordinator will confirm that the AEs are correctly entered into the AE log. The Study Monitor will confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies, as required.

11.1.5 Monitoring Activities

A safety monitor who is not a study investigator (see section 9.9.1) will conduct safety monitoring after treatment is complete for subjects 1, 5, 10, and 21. Adverse events will be documented and reported as described above.

The following issues will be addressed quarterly or more frequently as necessary:

- Verify receipt of all documents and supplies needed to conduct study
- Informed consent obtained for each participant
- CRF completion
- Investigational product accountability
- Check and review of the regulatory binder and all essential documents
- Clinical supply inventory
- SAE reporting
- Enrollment issues and targets
- Protocol amendment and their approval by the IRB
- Significant protocol deviations
- Personnel changes
- Updated regulatory documentation
- Any other issue as deemed important to the conduct of the study

11.1.6 Study Closure

Upon study closure a final evaluation of the data will ensure that all forms are present and complete. Data will be maintained in a secure location for

the appropriate duration as described in section 10.5. At the conclusion of this term, all forms will be shredded and destroyed. All subjects will be contacted via phone to thank them for their participation and to discuss the study findings as well possible additional treatment options.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

12 Ethics

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, the relevant federal regulations, and IRB policies and procedures and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB according to its policies and procedures.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of all subjects will be sought using the IRB-approved consent form. Before a subject undergoes any study procedure, an informed consent discussion will be conducted and written informed consent obtained with a consent form signed by the subject or legally acceptable surrogate if applicable. An investigator-designated research professional will obtain written informed consent from subjects. All subjects will be given a signed copy of the informed consent form.

13 Study Finances

13.1 Funding Source

The study is funded by a grant from Medtronic Sofamor Danek USA, Inc.

13.2 Conflict of Interest

Any investigator who has a conflict of interest (COI) with this study as defined by the policies of the UNC IRB will have the conflict reviewed by a properly constituted Conflict of Interest Review Committee with a committee-sanctioned conflict management plan that has been reviewed and approved by the IRB prior to participation in this study. All investigators will follow the UNC conflict of interest policy.

13.3 Subject Stipends or Travel Reimbursements

Subjects will not be remunerated for study participation.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study will be obligated to provide the sponsor with complete test results and all data derived from the study.

15 Device Instructions For Use (IFU)

Study Device-**Gel-Bead Microsphere; OptiSphere embolization spheres**

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