Study Title: Geniculate Artery Embolization for the Treatment of Knee Osteoarthritis
04/08/2025

G190248 Supplement 001

A. Cover Page

Device Information :
Device name:
Teleflex Gel-Bead

Intended use of device:
The Gel-Bead embolization particles will be used to perform geniculate artery embolization (GAE) for the purposes of treatment of osteoarthritis-related knee pain.

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Sponsor-Investigator and Correspondent Contact Information:
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Manufacturer Information:
Teleflex (acquired Vascular Solutions, Inc. February
2017) 3015 Carrington Mill Boulevard
Morrisville, NC 27560
Tel: 919-544-8000

Distributed by Medtronic

Referenced files: There are no referenced files.

Protocol Ammendments:
Updated protocol to remove 6-minute walk test due to feasibility issues in performing

B. Clinical Plan

The primary goal of our investigation is to determine if geniculate artery embolization (GAE) will result in a decrease in pain and disability caused by knee osteoarthritis. The investigation will be conducted as two distinct studies:

1. A pilot study of GAE for the treatment of knee osteoarthritis
a. A series of up to 30 subjects undergoing geniculate artery embolization will be included in this arm with the explicit purpose to demonstrate safety and efficacy.

The primary endpoint of this study is overall efficacy of treatment as determined by a minimal clinically significant improvement in KOOS pain score of 10 based on the KOOS Pain questionnaire at 6 months.

Secondary outcomes will be improvement in functionality and quality of life based on the KOOS Function in Sport and Recreation, and KOOS Quality of Life Scales. Secondary outcomes will also include changes in quantitative functional metrics as well as reduction in medication use.

Technical success will be defined as the performance of diagnostic angiography of the knee with delivery of the Gel-Bead particles to a region of hypervascularity within the knee resulting in reduced flow/occlusion of the target vessels. Clinical success will be defined by a decrease in pain of 10 points per the KOOS questionnaire at 6 months.

C. Report of Prior Investigations of the Device

Name of the Investigational Device: Gel-Bead Microspheres

Intended Use of the Device: Geniculate artery embolization (GAE) for patients with osteoarthritis of the knee.

Description of the Investigational Device
Gel-Bead embolization spheres were found to be substantially equivalent and cleared medical devices (Premarket Notification K133237) to prior technologies:

- Embosphere Microspheres (Biosphere Medical, Inc/Merit Medical Systems, Inc, K021397)
- 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 is intended for use in embolization of hypervascular tumors.

Gel-Bead embolization spheres (Gel-Bead) consist of biodegradable gelatin spheres pre-filled in 20ml syringes. Each syringe contains 1 ml of spheres suspended in 5 ml of saline. There are four size ranges for Gel-Bead offered: 100-300 um, 300-500 um, 500-700 um and 700-1000 um. The spheres are intended to be delivered via a delivery catheter with an inner diameter that is appropriately sized for sphere delivery (not included). The product is intended for single use and is sterilized by Gamma irradiation. The liquid suspension is mixed with iodinated contrast before use to allow visualization under fluoroscopy. Once a catheter has been fluoroscopically guided into the target vessel, the microspheres are injected and cause obstruction at the arteriole level until the desired degree of

embolization is reached. The microspheres used during this study will be unmodified.

A Gel-Bead implantation GLP animal study in twelve mature miniature swine, with animals survived up to 12 weeks following implantation was performed (13). Eight animals received Gel-Bead and four animals were implanted with the control (Embosphere). Gel-Bead spheres were implanted in the selected target arteries with angiography confirmation. 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. No clinically significant abnormalities were identified in the clinical pathology blood results. No systemic abnormalities were identified. Verification, animal study, and biocompatibility test results met the specified acceptance criteria and did not raise new safety or performance issues. Gel-Bead was therefore deemed substantially equivalent to the predicate device (Embosphere).

The technological differences between the Gel-Bead and predicate device have been evaluated through bench tests to provide evidence supporting the substantial equivalence of the 100-300 μm and 300-500 μm size embolization spheres. The 100-300 μm and 300-500 μm sizes are substantially equivalent to the specified predicate device based on comparisons of the device functionality, technological characteristics, and indications for use. The device design has been verified through the following tests: deliverability, sphere diameter, sphericity. Gel-Bead received 510(k) clearance from the FDA in April 2014 for the user of embolization of hypervascular tumors. Early trials have shown transcatheter embolization of abnormal neovasculature with particles can be effective in the treatment of mild to moderate knee osteoarthritis refractory to conservative management in select cases (5).

Transcatheter arterial embolization with microparticles has been shown to be safe in early trials for treatment of knee osteoarthritis as well as in patients being treated for hemarthrosis, with small trials showing no major complications related to particle embolization (5, 8-9). Additionally, complications do not increase with repeat embolizations (9). A theoretical advantage of Gel-Bead is the biodegradable nature, in contrast to other permanent microsphere devices, which remain permanently inside the patient.

Bibliography

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.

Guevara CJ, Lee KA, Barrack R, Darcy MD. Technically Successful Geniculate Artery Embolization Does Not Equate Clinical Success for Treatment of Recurrent Knee Hemarthrosis after Knee Surgery. J Vasc Interv Radiol. 2016 Mar;27(3):383-7.

Van Baardewijk LJ, Hoogeveen YL, van der Geest ICM, Schultze Kool LJ. Embolization of the Geniculate Arteries Is an Effective Treatment of Recurrent Hemarthrosis Following Total Knee Arthroplasty That Can Be Safely Repeated. J Arthroplasty. 2018 Apr;33(4):1177-1180.e1.

www.accessdata.fda.gov >pdf13. Gel-Bead 510(k) summary

D. Investigational Plan

1.0 Purpose of the Investigation

Osteoarthritis is an increasingly prevalent disease and often results in functionally limiting joint pain. In 2015, an estimated 54 million adults (22.7%) in the United States had doctor-diagnosed arthritis, with 43.5% of those patients reporting lifestyle and activity limitations (1).

The knee is a commonly affected joint and results in an annual healthcare expenditure of $27 billion (2). Definitive therapy for knee osteoarthritis is total knee arthroplasty. An estimated 54% of patients with knee osteoarthritis require a total knee arthroplasty within their lifetime, and 658,000 people undergo surgery annually (2-3). The goal of conservative management is to delay or eliminate the need for a total knee arthroplasty in patients. Currently, patients manage their pain with conservative management for an average of 13 years (2).

First line conservative management is treatment with physical therapy, weight loss, non-steroidal anti-inflammatory medications, and corticosteroid injections. Opiate medications are being prescribed with increasing frequency, despite evidence that they do not effectively treat osteoarthritis pain (4).

Early trials have shown transcatheter embolization of abnormal neovasculature with microparticles can be effective in the treatment of mild to moderate knee osteoarthritis refractory to conservative management in select cases (5). This therapy aims to treat the angiogenesis and inflammatory component involved in the pathophysiology of osteoarthritis (6-7).

Thickening and hypertrophy of the knee synovium has a similar appearance on angiography to hypervascular tumors. Transcatheter arterial embolization with permanent and resorbable particles has been shown to be safe in early trials for treatment of knee osteoarthritis as well as in patients being treated for hemarthrosis, with small trials showing no major complications and 8-20% having minor self-resolving skin or puncture site complications (5, 8-9). Additionally, complications do not increase with repeat embolizations (9). The use of resorbable particles has a theoretical advantage as the particles will not permanently reside within tissue.

1.1 Trial Objective

The purpose of this study is to perform a pilot to determine efficacy of transcatheter arterial embolization of the geniculate arteries in treating knee osteoarthritis related pain using the Gel-Bead embolization particles. This trial will assess reduction in pain, functional improvement, and reduction of medication usage in patients with mild to moderate knee osteoarthritis who have failed conservative management.

2.0 GAE Study Clinical Protocol

2.0 Title and Version Date of Clinical Protocol:
Geniculate artery embolization for the treatment of osteoarthritis of the knee
Version date: 4/18/2023

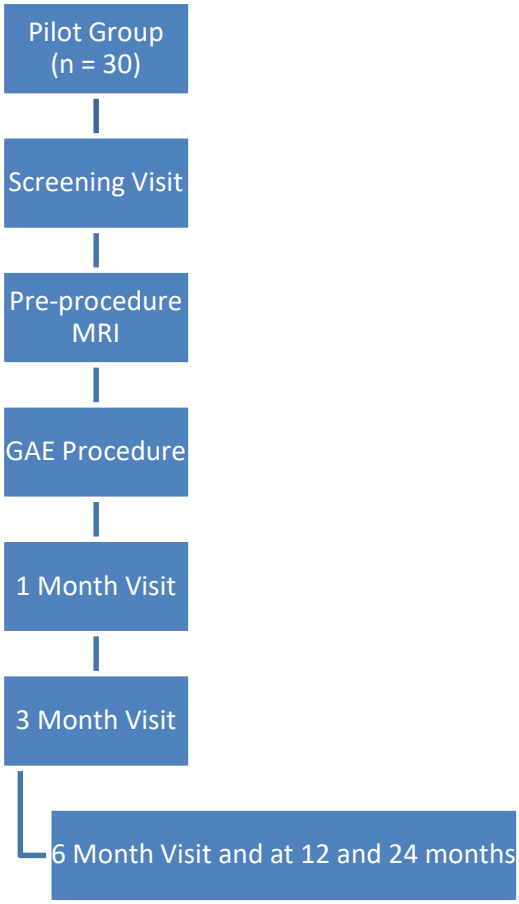
2.2 Study Design:

2.2.1 General Study Design
A series of 15 patients undergoing geniculate artery embolization will be included in this arm with the explicit purpose to demonstrate safety and efficacy.

This trial will assess reduction in pain, functional improvement, and reduction of conservative medical therapy in patients with mild to moderate knee osteoarthritis who have failed conservative

management, for 6 months and for up to two years following embolization.

2.2.2 Study Design Schematic



2.3 Subject Selection:

2.3.1 General characteristics of the proposed subject population

Similar to prior studies conducted on GAE, subjects included in the study will be those with mild to moderate knee osteoarthritis with moderate to severe pain that is refractory to conservative management. These are patients who have significant symptoms but are not ideal candidates for total knee replacement.

2.3.2 Anticipated number of research subjects

For the Pilot Study, 30 patients are expected to enroll (defined as completion of the informed consent process as per University IRB policies) and all are expected to complete the study.

2.3.3 Inclusion Criteria:

1. Patients between ages 18 and 75 with moderate/severe knee pain secondary to primary osteoarthritis. Moderate/severe pain will be defined as pain 30 mm to

100 mm on the Visual Analog Pain Scale (where 0 denotes 'no pain' and 100 mm denotes worst pain imaginable')

2. Grade 1, 2, or 3 osteoarthritis on the Kellgren-Lawrence grading scale on knee x-ray in the last 12 months
3. Pain must be refractory to 3 months of medical management (which may include a combination of oral analgesics, intraarticular steroids, viscosupplementation, opioid therapy, etc)
4. Patients willing and able to consent to the study

2.3.4 Exclusion Criteria:

1 Kidney dysfunction defined as an estimated GFR < 60 mL/min
2 Acute knee injury
3 Current local infection
4 Prior ipsilateral knee replacement surgery
5 Infectious or inflammatory arthritis
6 History of contrast allergy resulting in anaphylaxis
7 INR (International Normalization Ratio) > 1.6
8 Platelets < 50,000
9 Significant atherosclerosis that would limit angiography
10 Active malignancy
11 Active pregnancy
12 Appropriate candidate for knee replacement surgery determined by clinical and physical examination
13 Recent within 3 months, or active cigarette user
14 Any other condition that in the opinion of the investigator would preclude the patient from participation.

2.4 Study Procedures:

2.4.1 Patient Recruitment:

Patients will be recruited from sports medicine, family medicine, orthopedic, geriatric, and rheumatology clinics. Participating clinicians and research partners will identify patients with moderate or severe pain secondary to primary osteoarthritis (using the Kellgren-Lawrence Scale) who have persistent knee pain refractory to all attempted medical therapies and lifestyle modifications. The clinician will notify one of the GAE research team members. The patient will then be scheduled for consultation in the Interventional Radiology (IR) clinic. A thorough description of the research study will be provided. Informed consent will be obtained at this visit for any patient who chooses to participate. Pre-procedure work-up will also take place at this time (see below). Once the bloodwork and imaging are reviewed, the patient will be scheduled for the procedure following this clinic visit if they meet criteria and the patient is willing to proceed.

Visit 1 - Screening:

The screening period may take up to 8 weeks to complete. Some of the tests and assessments will be performed at the time of the consultation in Interventional Radiology (IR). Other tests and assessments

will be scheduled at appropriate facilities within the 8-week period. The following will be performed for screening:

1) Obtain informed consent
2) Collect demographics including age, sex, and race
3) Medical history and co-morbidities
4) Physical exam to include height, weight, BMI and vital signs
5) Evaluation for moderate sedation
6) Knee MRI with or without contrast. If performed within 12 months will not need to be repeated. Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire
7) Frequency/dosage of analgesic questionnaire
8) 100 mm visual analog pain scale
9) Knee x-ray. If performed within 12 months will not need to be repeated.
10) 30 second chair stand test
11) Pre-procedure labs – If performed within 1 month will not need to be repeated:
    - CBC with Platelets
    - GFR
    - INR
    - PTT

Pregnancy test for women of child-bearing potential

Remote consenting may be used as opposed to in person consenting where possible to reduce unnecessary in person encounters. In the event remote consenting is utilized, subjects will be provided with a copy of the informed consent prior to the teleconsent meeting either via email, fax, mail or previously provided during an in-person visit. After the physician investigator and subject review the consent form via video conferencing (e.g., telephone, conference call, videoconference, telemedicine, etc.), the subject will be offered the opportunity to ask any questions and have those questions answered. The subject will sign and date the informed consent.

The physician investigator will verify the subject physically signed the consent document either by viewing via video conference or obtaining a photo of the complete signed consent signature page or obtaining verbal confirmation from the subject that he/she signed the consent form or agreed to participate electronically. The signed document is then mailed, emailed, photo/scanned to text or faxed to the study team.

If the signed consent is provided as an electronic copy (emailed, photo/scanned, or faxed), the subject will return the original signed document on their first in person visit or by mail. If the signed consent form is mailed to the study team, the physician investigator will sign their copy which they possess after the subject has acknowledged signature on their copy. Once the subject's original copy is received the study team's copy will be attached to make a single document.

The study team will document the remote consent process, including the date and time the conversation occurred, how it occurred (e.g., telephone, video conference), the names of the participants, confirmation that the subject received the informed consent, and confirmation of informed consent to participate.

Visit 2 GAE Procedure:

Subjects should withhold pain medication 24 hours prior to visit for the evaluation of VAS or other measures.

Subjects will be treated with a genicular artery embolization (GAE) procedure performed with Gel Bead 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.

Subjects will not initiate new pain therapy or escalate current therapy for 1 month prior to GAE. A dose of intravenous antibiotic will be given in the peri-procedural period and oral antibiotics may be continued for up to 7 days. Anti-inflammatory medications will also begin 1 day prior to and up to 7 days after the procedure.

On the day of the procedure, the subject will be brought to the angiography suite and positioned in the supine position. Anxiolytic medications and analgesics will be administered per patient and provider discretion. After appropriate local anesthesia, arterial access will be obtained using a standard micropuncture kit. The femoral artery ipsilateral to the affected knee will be catheterized. A subsequent angiogram will be used to identify abnormal neovascularization arising from the geniculate artery branches. The affected geniculate artery branches will be catheterized with a microcatheter and the abnormal vessels will be embolized with a suspension of the Gel-Bead particles ranging in size from 100 to 500 micrometers at the physician's discretion. The suspension will slowly be injected into the vessel until there is stasis of forward flow. All guidewires, catheters and microcatheters will be removed. Hemostasis will be obtained either with manual compression or a closure device.

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.

Post-procedure Care and Disposition:

Following the procedure, the patient will be observed in the post-procedure area. Routine post-angiography care will be provided and routine precautions followed (lying flat for up to 6 hours post procedure, adequate post-procedure hydration with intravenous fluids). No additional lab work will be routinely drawn at this time. Any additional labs drawn will be left to the discretion of the attending physician. All complications, minor and major, will be documented and managed appropriately at the physician's discretion. Patient may be deemed appropriate discharge on the same day if:

1. There are no access site complications (e.g. groin hematoma)
2. Pain is adequately controlled
3. Patient is ambulatory
4. Distal perfusion to the bilateral lower extremities is confirmed by physical examination and/or Doppler waveforms
5. There are no signs of active bleeding or hemorrhage
6. Patient has a safe ride home

After GAE, follow-up will occur at 1 week (± 4 days), 1 month (± 2 weeks), 3 months (± 2 weeks), 6 months (± 2 weeks) from the date of treatment.

Visit 3 – 1 week (± 4 days) Post Procedure Phone Call

One week after the GAE procedure, a phone follow-up call will be made to check the on status of the subject. Standard post surgical questions pertaining to infection and pain will be asked. If there are any concerns, an in-person evaluation will be scheduled.

Visit 4 – 1 month (± 2 weeks) Post Procedure

Subjects will have the following assessments performed:
- Physical examination including vital signs
- KOOS and VAS questionnaires
- 30 second chair stand test
- Review of adverse events

Visit 5 – 3 months (± 2 weeks) Post Procedure

Subjects will have the following assessments performed:
- Physical examination including vital signs
- KOOS and VAS questionnaires
- 30 second chair stand test
- Review of adverse events

Visit 6 – 6 months (± 2 weeks) Post Procedure

Subjects will have the following assessments performed:
- Physical examination including vital signs
- KOOS and VAS questionnaires
- 30 second chair stand test
- Review of adverse events

Whenever possible, follow-up phone calls\tele-medicine visits will be made to subjects at 12 and 24-months post procedure to obtain updated information on pain.

2.4.2.1 Study Compliance

Subjects will be required to avoid escalation of conservative therapy during the study period. A review of current and prior conservative treatment measures will be reviewed with each subject during follow-up visits. Any patient that significantly elevates conservative therapy (e.g. initiation of a new medication or therapy not previously used) will be withdrawn from the study.

Early Withdrawal of Subjects:

Subjects will be withdrawn from the study under the following conditions:

1. At any point at the patient's discretion
2. Any major complication that occurs that prevents the ability to perform/complete the GAE procedure
3. Patient is unable to complete at least one follow-up visit

2.5 Statistical Methods and Data Analysis

2.5.1 Study Endpoints

2.5.1.1 Primary Endpoints

The primary endpoint of this study will be overall efficacy of treatment as determined by an improvement in pain of at least 10 points based on the KOOS Pain questionnaire at 6 months. The null and alternative hypotheses respectively will be: H_0: $Mean_{GAE} = Mean_{Sham}$ and H_A: $Mean_{GAE} \neq Mean_{Sham}$, with a two sided test.

2.5.1.2 Secondary Endpoints

Secondary outcomes will be improvement in functionality and quality of life based on the KOOS Function in Sport and Recreation KOOS, and Quality of Life Scale at 6 months as well as the quantitative functional measures and changes in medication use. To adjust for multiple comparisons, the Holm-Bonferroni correction method will be implemented.

2.5.2 Sample Size Determination

The Knee Injury and Osteoarthritis Outcome (KOOS) Score which is a primary outcome measure is a measure of patients' knee and associated problems and functionality. It is endorsed by the American Academy of Orthopedic Surgeons, the US Food and Drug Administration, and the International Cartilage Repair Society and has demonstrated reliability for both clinical and research purposes (11). The Visual Analog Scale (VAS) for pain will be used as a secondary outcome measure. This scale is also well-validated and has demonstrated reliability for patients with osteoarthritis (12). The Minimal Clinically Important Difference (MCID) for KOOS has been reported to be ~10. Data on the KOOS indicates a population standard deviation of 15 (koos.nu). Assuming we wish to detect an MCID of 10 points in this population, our targeted effect size is 0.66. A power calculation for a paired t-test (baseline vs 6-month KOOS Pain scores) shows our pilot study of 15 patients would have 22% power.

2.5.3 Efficacy Analysis

Comparison of semi-quantitative and quantitative outcome measures will be performed with the appropriate statistics testing. For the pilot group, baseline and endpoint scores will be compared using paired t-tests.

2.5.4 Safety Analysis

Differences in the occurrence of adverse events between groups will be assessed with chi-square tests with a significance level $p < 0.05$. Descriptive statistics will be used to report occurrence of adverse events in the pilot group.

3.0 Risk Analysis

3.1 Anticipated Risks

To mitigate risk to patient confidentiality, data will be kept in encrypted files on a secure UPMC server. The identifying patient information will be kept in a second document separate from the clinical data gathered, and a non-identifying code will be assigned to each patient. The data collected will not be shared with any person(s) not included in the study investigator list. Should a breach of conduct occur, the IRB will be notified immediately by one of the principal investigators.

Participants in the intervention arm will undergo an invasive procedure and will be subjected to moderate-to-high risk. Risks include but are not limited to bleeding at the puncture site, infection, damage to nearby structures, synovitis, worsening of groin hematoma, and nontarget embolization. A qualified, board-certified interventional radiologist will perform the procedure. Sterile technique will always be followed. Radiation exposure to the patient will be minimized using standard strategies (e.g. aggressive collimation, minimizing fluoroscopy time). All adverse events will be thoroughly documented and reported to the UPMC IRB immediately.

Because the study population has osteoarthritis-related knee symptoms refractory to conservative management, the next treatment option traditionally available is knee replacement surgery. Transarterial embolization, while still an invasive procedure, has a much lower risk profile that knee replacement surgery.

This trial will include 15 initial patients to confirm safety and initial efficacy of the treatment. Patients will include both male and female and range from age 18-75 who meet the inclusion criteria as detailed above. GAE will be performed by the trained investigating Interventional Radiologists who have significant experience in performing endovascular embolization procedures.

3.2 Adverse Event Recording/Reporting

3.2.1 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 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.

3.2.2 Eliciting Adverse Effect Information
Clinical subjects will be routinely questioned about adverse effects at study visits.

3.2.3 Recording and Assessment of Adverse Effects
All observed or volunteered adverse effects (serious or non-serious) and abnormal test findings, regardless of treatment group 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 casual relationship between the adverse effect and the investigational device or, if applicable, other study treatment or diagnostic product(s).

Adverse effects or abnormal test findings felt to be associated with the investigational device or 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.

3.2.3.1 Abnormal Test Findings

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 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 dosing or exposure or discontinuation of subject participation in the clinical study.
- The test finding is considered an adverse effect by the investigator-sponsor.

3.2.3.2 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.

3.2.4 Reporting of Adverse Effects to the FDA

The investigator-sponsor will submit a completed FDA Form 3500A to 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 3500Aas 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.

3.2.5 Reporting of adverse effects to the responsible IRB
In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the investigator-sponsor will report, to the IRB, any observed or volunteered adverse effect that is determined to meet all of the following criteria: 1) associated with the investigational device or, if applicable, other study treatment or diagnostic product(s); 2) a serious adverse effect; and 3) an unexpected adverse effect. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse effects will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator-sponsor's receipt of the respective information. Adverse effects which are 1) associated with the investigational drug or, if applicable, other study treatment or diagnostic product(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the investigator-sponsor's receipt of the respective information.

Follow-up information to reported adverse effects will be submitted to the IRB as soon as the relevant information is available. If the results of the sponsor-investigator's follow-up investigation show that an adverse effect that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the investigator-sponsor will report the adverse effect to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

3.3 Withdrawal of Subjects due to Adverse Effects

During evaluation of subjects and visits after the procedure, any adverse effects due to treatment will be evaluated and monitored. Subjects will not be withdrawn from the study due to adverse effects.

4.0 Description of Investigational Device:
Trade Name: Gel-Bead
Common / Usual Name Embolization spheres
Classification Name Class II – 21 CFR 870.3300;
KRD – Device, vascular, for promoting embolization
Predicate Device Gel-Bead embolization spheres, Vascular Solutions
(K133237 cleared April 25, 2014; K171946 cleared October 25, 2017)

Gel-Beads are embolic particles made from purified porcine skin gelatin. The product is crosslinked with glutaraldehyde, which improves the mechanical strength of the spheres and provides controlled degradation over time. These particles are intended for embolization of hypervascular tumors.

The embolization spheres product consists of biodegradable gelatin spheres pre-filled in a 20 ml syringe. The syringe contains either 1 ml or 2 ml of spheres suspended in 5 ml or 4 ml of saline, respectively. Offered in five nominal size ranges (100-300 μm, 300-500 μm, 500-700 μm, 600-800 μm, and 700-1000 μm), 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.

The technological differences between the subject and predicate device have been evaluated through bench tests to provide evidence supporting the substantial equivalence of the 100-300 μm size embolization spheres. The 100-300 μm size is substantially equivalent to the specified predicate device based on comparisons of the device functionality, technological characteristics, and indications for use. The device design has been verified through the following tests: deliverability, sphere diameter, sphericity.

The verification test results demonstrate that the Gel-Bead embolization spheres (100-300 μm) met the specified acceptance criteria and did not raise new safety or performance issues. Therefore, the 100-300 μm embolization spheres product is substantially equivalent to the predicate devices.

For additional device details refer to Appendix 1 of the IDE application for Vascular Solutions' 510k summary for the Gelbead embolization spheres and Appendix 2 of the IDE application for the instructions for use.

5.0 Monitoring Procedures:

Independent monitoring of the clinical study for clinical protocol and IDE application compliance will be conducted periodically (i.e., at a minimum of annually) with assistance from qualified staff of the University of Pittsburgh's Education and Compliance Support – Human Subject Research (ECS-HSR).

The investigator-sponsor and the University of Pittsburgh and University of Pittsburgh Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A data and safety monitoring plan will be implemented by the Principal Investigator (PI) to ensure that there are no changes in the risk/benefit ratio during the study and that confidentiality of research data is maintained. Each member of the study team will meet with the PI and review confidentiality issues and complete a confidentiality agreement, prior to having access to the identifiable medical record information. Investigators and study personnel will meet monthly to discuss the study (e.g. study goals and modifications of those goals; data collection; progress in data coding and analysis; documentation, identification of adverse events; violations of confidentiality) and address any issues or concerns at that time. Minutes will be kept for these meetings and will be maintained in the study regulatory bonder. Any instances of adverse events will be reported immediately to the University of Pittsburgh IRB using standard forms and/or procedures that have been established by the IRB. The IRB renewal for this study will include a summary report of the Data and Safety Monitoring Plan findings from the prior renewal period.

The Sponsor-investigator (Anish Ghodadra, MD) will be responsible for the monitoring of the study.

6.0 Labeling
Refer to section K. of the IDE application.

7.0 Consent Materials
Refer to Appendix 3 of the IDE application.

8.0 IRB Information
Refer to Section H. of the IDE application.

9.0 Other Institutions
Refer to Section I. of the IDE application.