Clinical Evaluation of a Vascular Venous Anastomotic Connector for Minimally Invasive Connection of an Arteriovenous Graft for Hemodialysis [InterGraft Study]

INVESTIGATIONAL PLAN

IDE # G140221

Investigational Plan Revision History:

Rev 1, October 10, 2014: Initial release, for IDE submission.

Rev 2, January 30, 2015: Added details of statistical analysis, sample size, electronic data capture.

Rev 3, June 2, 2015: Added independent Medical Monitor; revised Table 1 to clarify that Transonics device or similar method may be used for graft flow rate evaluation, added lab tests; added note that AIG may only be used after VIG has first been placed; added Table 2 to summarize study enrollment; clarified that pregnancy test is required to confirm subject is not pregnant at time of enrollment.

Rev 4, August 31, 2015: Added note to Inclusion criterion #7 that as required by an IRB, adult individuals who lack capacity to consent for themselves will be not be included in the study.

Rev 5, July 27, 2017: Incorporated information provided in Study Operations Memos 1-8.

Rev 6, November 14, 2018: Incorporated adaptive modification to the study design; added an independent DSMB, incorporated information in Study Operations Memos 9-13. NOTE: Effective with this revision, the InterGraft Arterial Anastomotic Connector (AIG) study device will no longer be used in the study. Reference to the AIG in this revision 6 of the Investigation Plan refers only to previously enrolled subjects in which an AIG was used.

Rev 7, May 29, 2019: Incorporated study design modifications, including clarification of the primary analysis population, sample size, planned enrollment, and statistical analysis modifications; revised 2-week follow up window in Table 1.

Rev 8, July 28, 2020: Changed total roll-in subjects from 12 to 15, study sites participating from 20 to 23 and maximum total of enrolled subjects (including roll-ins) from 170 to 173.

Sponsored by:

Phraxis, Inc.
Minneapolis, MN USA

Clinical Trial Registration:
NCT02532621

TABLE OF CONTENTS

ACRONYMS AND ABBREVIATIONS

AE	Adverse Event
AIG	Arterial InterGraft Connector
AV	Arteriovenous
AVG	Arteriovenous graft
CEC	Clinical Events Committee
CRF	Case Report Form
DCC	Data Coordination Center
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
ESRD	End Stage Renal Disease
GCP	Good Clinical Practice
IFU	Instructions for Use
IRB	Institutional Review Board
KDOQI	Kidney Disease Outcomes Quality Initiative (National Kidney Foundation)
MM	Medical Monitor
ePTFE	expanded Polytetrafluoroethylene
UADE	Unanticipated Adverse Device Effect
VIG	Venous InterGraft Connector

1.0 GENERAL INFORMATION

Study Name: Clinical Evaluation of a Vascular Venous Anastomotic Connector for Minimally Invasive Connection of an Arteriovenous Graft for Hemodialysis [InterGraft Study]

Study Device: The device evaluated in the study is the *InterGraft™ Venous Anastomotic Connector* (VIG).

Study Device Regulatory Status: Investigational Device. Limited by Federal (United States) law to investigational use.

Indication for Use: (proposed) The InterGraft™ Venous Anastomotic Connector provides a minimally invasive, sutureless method for attachment of an arteriovenous graft to a vein in the upper extremity. The InterGraft™ Venous Anastomotic Connector facilitates creation of the arteriovenous graft connection to a vein in support of hemodialysis in subjects with End Stage Renal Disease. The InterGraft™ Venous Anastomotic Connector is used together with conventional suturing of the arterial anastomosis to facilitate creation of an arteriovenous graft in support of hemodialysis in subjects with End Stage Renal Disease.

Study Design: Prospective, multicenter, non-randomized design

Subjects: A total of up to 173 subjects with ESRD who have a planned arteriovenous graft implant procedure for hemodialysis access and who meet the study selection criteria will be included.

Lead Principal Investigator:
John R. Ross, MD
Orangeburg, SC
Phone/email: (803)533-7544/ jrrsurgery@aol.com

Sponsor:
Phraxis, Inc.
Saint Paul, MN
Sponsor representative: Cindy Setum, Ph.D., Director of Clinical Affairs
Phone/email: (612) 801-6730/ csetum@phraxis.com

Data Coordination:
Clinical Development Associates, Inc.
Richmond, VA
Contact: Suzanne Cowley Phone/email: (804)-740-3363/ cowley1@rcn.com

Statistical Analysis:
Richard G. Holcomb, PhD
Minnetonka, MN
Phone/email: (952)745-0555/ rgholcomb2@cs.com

Medical Monitor:
Arif Asif, MD
Neptune, NJ
Arif.Asif@HackensackMeridian.org

DSMB Chairman:
Anthony Comerota, MD
Alexandria, VA
Anthony.comerota@Inova.org

2.0 INTRODUCTION and BACKGROUND

End Stage Renal Disease (ESRD) is a significant and growing health problem. In the United States (U.S.), 571,000 ESRD subjects underwent treatment in 2009; and since 2000, a 12% increase in the incidence rate of ESRD has been observed in subjects ≥ 75 years of age.[1] By the year 2020, the number of dialysis subjects is expected to reach 774,000, with an annual incidence of more than 160,000 new subjects per year. These subjects typically undergo three hemodialysis treatments per week, each lasting 3-4 hours. An arteriovenous (AV) vascular access is needed to remove blood for dialysis filtration and return to the body. The access must provide high blood flow volume continuously during treatment. Due to the need for surgical healing and development, the access is ideally prepared several weeks or months in advance of anticipated need. A significant challenge in managing ESRD subjects is providing access when needed, along with consistent and sustained access.

Vascular access has frequently been referred to as the "Achilles heel" of dialysis because of the high morbidity and mortality rates due to infection, thrombosis and ultimate access failure. Of the three types of vascular access: fistulas, grafts, and central venous catheters, the type used is influenced by factors such as the expected time course of renal failure and the condition of the subject's vasculature. While fistulas are considered as the gold standard, synthetic grafts are also widely used since fistulas cannot always be successfully established.[2] The failure rate of fistulas to mature and thus be suitable for dialysis may be as high as 60%.[3] Many patients will require an AV graft (AVG) access at some point during the disease course.[4] The creation of long term dialysis access remains a significant challenge, especially in patients with multiple prior failed access sites and in the elderly.[5-7] Indeed, with continued treatment of an increasingly older ESRD population, the increased use of AVGs may also be required.[8,9]

Grafts are relatively easy to place surgically using standard techniques. Expanded polytetrafluoroethylene (ePTFE) is the most common graft material.[4] Novel self-sealing multilayered ePTFE configurations and other graft materials (e.g., polyurethane) have recently been introduced, offering the potential for earlier access.[10,11] Compared with fistulas, AVGs have a greater incidence of recurrent stenosis, especially at the venous anastomosis, and require more salvage interventions to maintain patency for dialysis.[4] The pathogenesis of venous stenosis is comprised of a cascade of events resulting in endothelial and smooth muscle injury that results in intimal hyperplasia and ultimately flow limiting occlusion.[12] With the conventional end-to-side venous anastomosis, the vessel wall is subjected to turbulent, nonlinear flow and low shear stress at the toe and heel of the anastomosis, sites that correspond to the development of intimal hyperplasia. As hyperplasia progresses, increasing stenosis occurs resulting in a decrease in blood flow, leading to thrombosis. In addition to these hemodynamic factors, the trauma of surgical graft implantation due to relatively large (3-6cm) incision sites and circumferentially sutured anastomoses, contributes to increased healing time and possible complications. These findings point to the need for new devices and techniques to optimize AVG flow dynamics and healing, resulting in the reduction of stenosis and other complications.

Despite planning, a large percentage of patients present with an urgent need for hemodialysis and lack sufficient time to allow a fistula or standard surgical graft to be firmly established. In such cases, the use of temporary venous catheter access is the only option currently available. More than 80% of subjects will begin dialysis with a catheter and approximately 28% will use a catheter for permanent access.[1] Catheter use even for short periods can result in higher rates of infection, thrombosis, morbidity and mortality, compared to patients who do not start dialysis with a catheter.[12] Both the Fistula First Initiative and the KDOQI guidelines have established a goal to limit chronic catheter use to less than 10% of dialysis patients.[2,13]

While recognizing that a native fistula is the recommended access for hemodialysis, AVGs remain a frequently used access type. The InterGraft™ Venous Anastomotic Connector (VIG) was developed for minimally invasive venous anastomosis of a standard hemodialysis graft. This study will evaluate the safety and performance of the VIG for anastomosis of a commercially available, 6 mm diameter, ePTFE hemodialysis graft. Anastomoses with the VIG may potentially reduce venous vessel trauma, improve the local vessel wall shear stresses and promote laminar flow, thereby improving patency.

The original investigational InterGraft Clinical Study conducted under the approved IDE #G140221 was configured as a pivotal, prospective, multicenter, non-randomized, adaptive design. The study was intended to enroll up to 252 subjects including roll-in subjects, subjects in whom both a VIG and AIG were used, and a small VIG sub-study of subjects who did not qualify for treatment with the AIG. Subject enrollment began on November 12, 2015. The study recruitment rate was slow and attributed primarily to challenges in identifying subjects with a suitable artery for using the AIG. Initial investigator feedback indicated that the AIG was cumbersome to deploy and would not likely be adopted by clinicians in its current design. The study was subsequently modified to discontinue further study of the AIG and all future enrolled subjects were to be treated using a VIG and sutured arterial anastomosis for AVG implantation. In accordance with the original investigational plan, in July 2018, an interim analysis was performed after the first 52 subjects receiving treatment with the VIG +AIG were enrolled and follow-up was completed.

Investigator feedback, safety data and device performance data (number and type of reported device malfunctions) from the first 52 subjects treated with a VIG and AIG (interim analysis population) were evaluated and the results were used to inform the modified study design described in the previous revision 6 of the Investigational Plan.

With this current Investigational Plan, the study primary analysis population will now include the following:

- All USA subjects enrolled since June 5, 2018 and treated with the VIG + sutured arterial anastomosis (These subjects were not included in the interim analysis.)

- All USA VIG sub-study subjects enrolled after October 17, 2017 (These subjects were not included in the interim analysis.)

Roll-in subjects, subjects who were included in the planned interim analysis that has previously been completed, and other subjects that received an AIG will not be included in the primary analysis population. However, these subjects will continue to be followed and evaluated according to the requirements of the current protocol, which are identical to the previous version protocol requirements, and these results will also be included in a final study report.

The current study will evaluate use of the VIG for placement of an AVG. The venous anastomosis will be created using the VIG and the arterial anastomosis will be created using standard suturing. The study focuses on subjects who have a failed fistula, cannot have a fistula, or are better suited for an AVG, as determined by the physician. The graft implant procedural outcomes, the number and type of major adverse events, and patency throughout a six (6) month follow-up period will be evaluated. The 6-month patency rate will be compared with a pre-

specified patency performance goal that is drawn from prior surgical AVG literature and published performance standards.[10, 14-20]

This study will be conducted in compliance with the Investigational Plan, Investigational Device Exemption (IDE) regulations, Good Clinical Practice guidelines (GCP), and other applicable regulatory requirements. The study Sponsor (Phraxis, Inc.) intends that the study results will support a 510(k) marketing clearance for the InterGraft Venous Anastomotic Connector.

3.0 STUDY DEVICE DESCRIPTION

The device evaluated in the study is the InterGraft™ Venous Anastomotic Connector (VIG). The VIG is designed for transcatheter delivery within a vein and connection to an AVG that has been tunneled under the skin in a standard manner. The connection is made via a small skin incision.

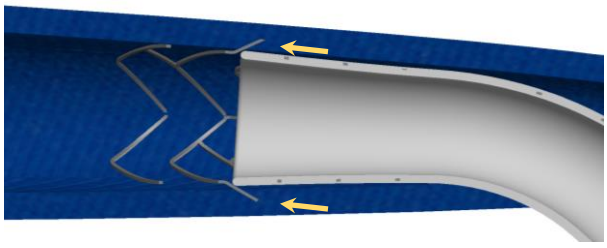
The VIG is constructed with a nitinol framework encapsulated with ePTFE in the midsection and uncoated at the ends (**Figure 1**). The VIG is delivered and deployed within the target vein using a customized transcatheter delivery system. The VIG is a flexible, flared, self-expanding endoprosthesis designed for coaxial placement in peripheral veins up to 10 mm in diameter. The distal flared end is configured as a nitinol scaffold with anchoring barbs that extend into the vein wall. The 'graft end' of the VIG is configured as a stent-like framework for anchoring within the ePTFE graft. The materials used in constructing the VIG are all medical-grade with well-established biocompatibility profiles.

The VIG is supplied pre-mounted within a customized transcatheter delivery system for over-the-wire delivery via an 11F vascular sheath. The VIG is intended as a permanent implant. The delivery system is a sterile, single use, disposable item. A detailed description of the VIG and delivery system is provided in the Instructions for Use (**Appendix A**).

Indication for Use

The InterGraft™ Venous Anastomotic Connector provides a minimally invasive, sutureless method for attachment of an arteriovenous graft to a vein in the upper extremity. The InterGraft™ Venous Anastomotic Connector facilitates creation of the arteriovenous graft connection to a vein in support of hemodialysis in patients with End Stage Renal Disease. The InterGraft™ Venous Anastomotic Connector is intended to be used together with conventional suturing of the arterial anastomosis to facilitate creation of an arteriovenous graft in support of hemodialysis in patients with End Stage Renal Disease.

Figure 1- InterGraft Venous Anastomotic Connector (VIG). Note barbs that anchor VIG within the vein (arrows).



4.0 PRIOR STUDIES

Both the VIG and an arterial InterGraft Connector (AIG) were evaluated in the prior testing and studies described below. The findings from the prior testing are also applicable to use of the VIG only. The AIG will not be used in the current study.

Bench Testing

Bench testing of the VIG confirmed the structural integrity of the device, adequacy of resistance to compressive forces and radial forces, adequacy of bond strengths, kink and migration resistance, and verification of critical dimensions. Where applicable, testing was conducted using commercial 6mm ePTFE grafts (C.R. Bard, Inc., Murray Hill, NJ) that were selected due to their current widespread clinical use.

Computational Fluid Dynamics (CFD) modeling of the VIG used together with AIG was performed, based on a 6 mm graft connecting artery and vein.[21] This modeling demonstrated resulting graft flows of approximately 1 L/min when the AV pressure difference was approximately 100 mm Hg. With graft flow rates ranging from 980 - 1100 ml/min, the maximum wall shear ranged from 265Pa - 180Pa, and thus below the threshold to cause mechanical hemolysis (800Pa), or that thought to stimulate hyperplasia.[21] These findings confirmed the acceptability of the InterGraft design for clinical evaluation.

Pre-Clinical Studies

Simulated use testing was performed for verification of the VIG deployment procedure. The VIG performed adequately for intended use with respect to the ability to access, deploy and withdraw.

Acute animal studies evaluated the deliverability of the VIG, the ability to complete an AV circuit using PTFE grafts, and near-term graft patency following initial placement of grafts using a VIG and AIG.[22] Testing was performed using a femoral artery/vein canine model. These studies provided evidence of safety and acceptable performance of the VIG.

Clinical Studies

First-in-Human Study

A first-in-human clinical evaluation of the InterGraft Venous and Arterial Connectors was performed.[23] The InterGraft Connectors were successfully used in 9/9 subjects for connection of an AVG in the upper arm: 5 subjects received both the VIG and the AIG, and 4 subjects received the VIG for the venous anastomosis and a standard sutured arterial anastomosis. InterGraft™ delivery and deployment success was obtained in all cases. All AVGs were patent at the end of the procedure.

AIG Adverse events occurred during the procedure in 3 subjects: (i) In one case, a successfully deployed AIG was inadvertently nicked with a surgical tool during closure of the incision site. This resulted in a hole in the ePTFE coating on the AIG, creating a blood leak path that could not be repaired. The AIG was removed and a sutured arterial anastomosis was prepared at the same arteriotomy site. There were no further sequelae. (ii) In another case, an acute graft occlusion occurred during the graft implant procedure. Angiographic examination showed that the tunneled graft had been positioned in a manner that caused a graft kink. Aspiration thrombectomy via a guide catheter was performed, the graft was re-positioned to relieve the kink, and graft flow was immediately restored. There were no further sequelae. (iii) In another case, persistent bleeding at the AIG arteriotomy site occurred and was attributed to an incomplete seal around the arteriotomy site. The cause was not determined but

could have been due to vessel wall damage during deployment, a coating defect on the AIG, or a mal-positioned AIG. The bleeding was remedied by placement of a single suture at the leak site, and there were no further sequelae.

There were no procedural adverse events related to the VIG.

All subjects were discharged within one day after the procedure with patent grafts. Grafts were used for hemodialysis within 17 days, on average, and temporary venous catheters were removed. Subjects were followed to six months. Three subjects exited the study early for reasons unrelated to the InterGraft devices. The remaining 6 subjects had patent grafts. It was concluded that the InterGraft connectors can safely and successfully be used for AVG anastomoses. An additional adverse event occurred in one subject after discharge: the subject had peritonitis and required abdominal surgery (not related to the study device). The subject developed a hospital-acquired infection and the graft subsequently became infected and was removed. Of the 8 remaining subjects/grafts, 7 were confirmed to be patent at one month following the implant procedure (primary patency). In the remaining subject, the one month follow-up has not yet been performed.

Investigator Feedback Collected During Enrollment of the First 52 Subjects in the IDE G140221 Clinical Study
As originally designed, the IDE G140221 clinical study included both an arterial InterGraft Connector (AIG) and a venous InterGraft connector (VIG). Investigator feedback collected during enrollment of the first 52 subjects indicated the following:

- A high level surgical/interventional skill was needed for AIG delivery and deployment;
- Identifying subjects with a target artery suitable for using the AIG was a key obstacle to enrollment;
- The anatomic requirements needed for proper positioning of the AIG relative to the artery orientation, to avoid kinks and untoward stresses to the implanted device were also obstacles to enrollment;
- Investigators noted that while the AIG can work, the current design/procedure is complex and not ready for widespread adoption;
- Several investigators appeared to have become disinterested in the study due to the above noted challenges, as evidenced by a very slow recruitment rate.

Based on this investigator feedback, Phraxis determined that the AIG in the present configuration with a relatively complex delivery and deployment procedure, is excessively challenging to use, and that even if cleared-to-market, the AIG would likely not be readily adopted by clinicians. Thus, Phraxis concluded that the AIG is not ready for commercial introduction and Phraxis decided to stop further study of the AIG. On August 9, 2018, investigators were notified to stop further study of the AIG, and to continue follow-up to 6 months in subjects that had previously received an AIG, in accordance with the investigational plan.

5.0 STUDY OBJECTIVE

The objective of the current study is to demonstrate that the 6-month cumulative patency of AVGs connected with the InterGraft™ VIG connector is similar to that of AVGs connected using standard sutured anastomoses.

6.0 STUDY DESIGN

This is a multicenter, prospective, non-randomized design study. All enrolled subjects will receive the VIG device and will have a standard sutured arterial anastomosis. The study allows for a maximum enrollment of 173 subjects, including a provision for 12 subjects lost to follow-up and up to 15 roll-in cases. Data from roll-in subjects will not be included in the primary analysis but will be analyzed separately.

The study includes up to 23 participating clinical centers. Study site investigators will be physicians skilled in AVG placement and interventional techniques. Study data will be collected up to the point at which each subject has completed the 6-month endpoint or experienced a terminal study endpoint.

7.0 SUBJECT SELECTION

The following inclusion and exclusion criteria must be met for enrollment in the study:

Initial Inclusion Criteria (All must be answered YES for study eligibility.)

1. Subject is ≥ 18 years of age.
2. Subject requires the creation of a vascular access graft for hemodialysis, secondary to a diagnosis of End Stage Renal Disease.
3. Subject is able to have the vascular access graft placed in an upper extremity.
4. Baseline imaging shows suitable vascular anatomy/ vessel size for the InterGraft™ Venous Connector and an artery at least 3.5 mm in diameter that is suitable for creating the arterial anastomosis.
5. Subject has a reasonable expectation of remaining on hemodialysis for at least 6 months.
6. Subject or his/her legal guardian understands the study and is willing and able to comply with the dialysis schedule and follow-up requirements.
7. Subject or his/her legal guardian provides written informed consent. NOTE: In accordance with the requirements of some Institutional Review Boards (IRB), where applicable, only those subjects with capacity to consent for themselves will be included. Thus, where required by the IRB, adult individuals who lack capacity to consent for themselves will be excluded from the study.

Final Inclusion Criterion to be applied at the time of surgery (Must be answered YES for enrollment into the study.)

8. Physician's examination at time of surgery shows no significant vessel lesions, calcification(s), anatomic structures or abnormalities that may limit ability to safely deploy the InterGraft™ Venous Connector or create a sutured arterial anastomosis.

Exclusion Criteria (All must be answered NO for study eligibility.)

1. Subject has a documented and unsuccessfully treated ipsilateral central venous stenosis as determined by imaging.
2. Subject currently has a known or suspected bacterial, fungal, or HIV infection. NOTE: Subjects with hepatitis B or C may be included in the study.
3. Subject has a known hypercoagulable or bleeding disorder or requires treatment with warfarin or heparin.

NOTE: The intent of this criterion is to exclude patients with high risk for bleeding or clotting complications. As such, patients who are taking oral anticoagulants (blood thinners) including, but not limited to, Xarelto® (rivaroxaban) or Eliquis® (apixaban) should also be excluded from the study. Patients may receive anticoagulation therapy any time after the study AV graft implant procedure, at their physician's discretion. This should be driven by an indication unrelated to the vascular access.

4. Subject has had a previous instance of Heparin Induced Thrombocytopenia type 2 (HIT-2) or has known sensitivity to heparin.
5. Subject has co-morbid conditions that may limit their ability to comply with study and follow-up requirements.
6. Subject has had >2 previous arteriovenous accesses in treatment arm.
7. Subject is currently taking Aggrenox®.
8. Subject needs or is scheduled for any major surgery within 30 days of the study procedure.
9. Subject is currently taking maintenance immunosuppressant medication such as rapamycin, mycophenolate or mycophenolic acid, prednisone (>10 mg), cyclosporine, tacrolimus or cyclophosphamide.
10. Life expectancy is less than 12 months.
11. Subject is pregnant. NOTE: A negative urine pregnancy test within 24 hours of the study procedure is required in all female subjects with reproductive capacity.
12. Subject is a poor compliance risk (i.e. history of IV or oral drug abuse).
13. Subject is enrolled in another dialysis or vascular investigational study.

8.0 STUDY ENDPOINTS

Primary Endpoint

The primary endpoint is cumulative patency at 6 months, defined as the percentage of subjects free from loss of access of the study graft for hemodialysis, assessed at 6 months.

Secondary Endpoints

Secondary endpoints for the study include:

1. Acute device success, defined as AV graft flow at the end of the procedure as determined by palpable graft thrill and/or audible bruit, without significant bleeding or emergent surgery.
   Primary Unassisted Patency at 6 Months, defined as the percentage of subjects free from the first occurrence of either access thrombosis or an access procedure performed to maintain access patency.
2. Time to First Cannulation, defined as the time from initial access placement to the first graft cannulation.
3. Number and type of interventions required to maintain secondary patency
4. Number and type of serious adverse events (SAEs) through 6 months. SAEs include the following: death, emergent surgery, infection requiring treatment (e.g., prolonged or intravenous antibiotic therapy), significant bleeding (defined as bleeding requiring treatment), and pseudoaneurysm.

Expected interventions for restoration of patency will be documented and reported separately, are reflected in the evaluation of cumulative patency, and will not be tabulated again as SAEs.

Endpoints will be evaluated acutely (at the time of implant), at time of any AVG intervention, at two weeks, and monthly through 6 months for all subjects. The study AVG patency evaluation starts immediately after the index procedure is completed (e.g., subject leaves the surgery suite). This means that once the AVG is created, patency evaluation begins. The occurrence of acute thrombus and treatment thereof during the index procedure while the vascular access is being created does not trigger the loss of primary patency.

9.0 SUBJECT SCREENING AND INFORMED CONSENT

Screening and Enrollment

All subjects referred for AVG implant should be screened for study eligibility. A member of the Research Team will evaluate the subject for eligibility. If all initial inclusion criteria are met and no exclusion criteria are present, a member of the Research Team should inform the subject about the study's purpose and should obtain written informed consent.

Final enrollment eligibility is determined at the time of surgery, after the physician has confirmed the final inclusion criterion is met. Enrolled subjects will be assigned a unique study subject identification number. Each study site will maintain screening and enrollment logs to record all subjects who were screened and all subjects who were enrolled. Reason for screen failures will be recorded. Screening log data will not be included in the primary database but will be reviewed during study monitoring.

No clinical site may contribute more than 25% of the total enrollment (excluding roll-in subjects).

Baseline Imaging

Angiographic or ultrasonic imaging of the target limb vasculature is routinely performed as part of determining the optimal AV access plan for a subject. As part of subject screening, baseline imaging should be reviewed to determine whether the subject meets the following criteria (as determined by the physician) for use of the VIG:

- General: Flow rate must be adequate for the creation of dialysis access, as previously mapped with ultrasound or angiography
- Vein inner diameter at planned anastomosis site is 4 -7 mm in luminal diameter
- Artery inner diameter at planned anastomosis site is at least 3.5 mm in luminal diameter

Informed Consent

A member of the Research Team will approach the subject to obtain written informed consent. The background of the study and the benefits and risks of procedures and the study should be explained to the subject. The subject (or their legal representative, if applicable) must sign the consent form prior to initiation of study procedures. The consent form must have been previously approved by the study site's IRB. Failure to provide consent renders the subject ineligible for the study. Subjects will be given a copy of the signed informed consent document. The signed informed consent will be retained with the study records at the site. It is the responsibility of the Investigator to assure that informed consent is obtained from each subject in accordance with the guidelines of the IRB and all applicable regulatory guidelines.

10.0 STUDY PROCEDURE

The procedure will be performed in accordance with the Instructions for Use (IFU) provided with the study device (**Appendix A**). A commercially available 6mm diameter synthetic graft will be used. Such grafts may include conventional ePTFE grafts or grafts designed for early cannulation (within 24-48 hours). The study procedure will be performed in an operating room that has fluoroscopic imaging capability for guiding placement of the VIG. The anesthesia regimen will be determined at the physician's discretion; there are no study-specific anesthesia requirements. A regional nerve block is typically performed for placement of an AVG. Standard, routine hemodynamic monitoring will be performed to assess cardiovascular status throughout the procedure. Heparin anticoagulation may be provided at the physician's discretion.

Small skin incisions will be made for tunneling the graft under the skin in a standard manner. The VIG device is provided pre-loaded within a customized catheter-based delivery system for over-the-wire delivery. The VIG is inserted through an introducer sheath placed in the target vein so that the 'vessel end' of the VIG is deployed within the vein, and the 'graft end' extends out of the vein for connection to the graft. Delivery and deployment will be performed under fluoroscopic guidance. The VIG will be deployed first, connected to the AVG, then the graft and VIG will be flushed and clamped. The arterial anastomosis will then be created using a standard suturing method.

NOTE: Although not expected, in the event that connection of the venous graft segment using the VIG is attempted but not able to be completed, the venous anastomosis should be completed using standard suturing. Such situations will be considered as a procedure failure.

Following establishment of the AV circuit, the skin incisions will be sutured closed using standard techniques. The subject will be moved to a recovery area for monitoring prior to discharge. It is anticipated that most subjects will be discharged the same day or within 24 hours following the AVG implant procedure.

Use of Clamps

To avoid mechanical damage or disruption to the AVG or VIG, surgical clamps or other tools with teeth or other sharp features should not be used during the AVG implant procedure. An atraumatic or guarded (e.g., rubber) clamp should be used for clamping the AVG, as needed. Do not clamp or manipulate the VIG with surgical tools. Use only gentle pinching with the fingers to hold the VIG and to control hemostasis.

Other Treatment Immediately after Deployment of the VIG

It is anticipated that no other interventional treatments will be required during the implant procedure. At the venous anastomotic site, no further treatment should be provided if the luminal diameter is $\geq$ 90% of the adjacent normal vessel, based on operator's assessment. If the luminal diameter is <90%, balloon angioplasty may be performed as follows:

After deployment, the nitinol-reinforced VIG *may* be smoothed and more fully seated against the vessel wall by inflating an angioplasty balloon. Balloon treatment should be performed according to the manufacturer's instructions, by a physician skilled in peripheral vascular interventional techniques. The balloon diameter used should be equal to that of the VIG diameter and should be no larger than 6mm when used to treat the VIG segment that is within the AVG. The balloon should be inflated within the VIG along the entire length. Multiple

inflations may be needed. To avoid possible displacement of the VIG, the physician should assure that the balloon is fully deflated prior to carefully removing the balloon.

Vascular Graft for Hemodialysis
Vascular grafts that meet the following requirements, as determined by the physician, may be used: commercially available, straight (not-tapered), 6 mm inner diameter ePTFE grafts. Adequate graft length and trimming must be carefully determined to facilitate optimal positioning after the venous and arterial graft anastomoses have been completed. The graft should never be too short.

Treatment of Ipsilateral Central Venous Stenosis Prior to Enrollment
Ipsilateral central venous stenosis is a study exclusion. However, a patient with central venous stenosis may be considered for the study following successful treatment of the stenosis. Central stenosis angioplasty may be performed first, then immediately followed with the study procedure. The patient may be enrolled if, as assessed by the investigator, the central stenosis has <30% residual stenosis, which is the KDOQI threshold for successful intervention. The patient should not be enrolled if the residual stenosis is >= 30% or if the investigator determines that the treatment could impact the ability to assess the study endpoints (e.g., acute device success, graft patency, safety).

Study Device Failure, Defect, or Suspected Device Problem
Device malfunction is defined as *any occurrence in which the study device does not perform as intended, when used or attempted to be used in a study procedure*. As described in the device Instructions for Use (IFU), a visual examination of the VIG should be performed at the time of opening the packaging and prior to use in a subject. Defective devices (obvious or suspected) should not be used. A replacement VIG should be obtained and the study procedure continued. A device accountability log will be used to account for all used and opened/unused devices in this study.

If a VIG defect or malfunction is discovered/suspected any time prior to vascular deployment, the VIG should not be used. A replacement device/component should be used and the study procedure continued. A Device Malfunction form must be completed for all device malfunctions, failures or suspected failures, and the defective product identification should be recorded on the device accountability log. Whenever possible, a defective/suspected defected VIG should be returned to the Sponsor for evaluation.

The Device Malfunction form (eCRF) should be used to report and provide details of situations in which the VIG does not perform as intended. Failure of the VIG to perform as intended may be potentially be due to a variety of reasons, including defect or suspected defect in the device itself or the delivery system; operator error; anatomic issues; or other reasons. If use of the VIG is attempted but ultimately the device is not able to be used, a Device Malfunction eCRF should be submitted to report the surrounding details.

NOTE: Device Malfunctions should reported on the Device Malfunction eCRF <u>within 24 hours of discovery</u>. 24-hour reporting of device malfunctions will assist with Sponsor's efforts to assess whether any SAEs associated with a device malfunction may also have occurred.

Bailout Procedure
Bailout procedures are not anticipated, but could potentially be required if, for example, the VIG does not deploy correctly, does not seal correctly, is not deployed at an acceptable location, or if there are any major vascular events. In such cases, the subject should be referred for surgical intervention. No attempt should be made to remove an improperly deployed VIG using percutaneous methods.

Assessment of Graft Flow at the End of the Study Procedure
An AVG placed using the VIG and a sutured arterial anastomosis typically has a pulse and/or thrill which is easily palpable over the skin or directly in the AVG prior to closure of the surgical incisions. Thus, the AVG flow assessment is similar that used for standard sutured AVGs. An optimal method to confirm AVG patency at the end of the implant procedure is to feel a thrill near the arterial anastomosis or confirm a Doppler signal. Ascultation using a sterile or covered stethoscope is also acceptable. At the physician's discretion and as warranted, a final angiogram may also be performed to verify patency of the graft.

Initial Use of the Study Graft for Hemodialysis
Initial hemodialysis cannulation of AVGs placed with the VIG should be performed in accordance with the graft manufacturer's Instructions for Use. After needle withdrawal, use gentle, non-occlusive digital pressure to compress the cannulation site until hemostasis is achieved. The VIG should NOT be directly cannulated. In accordance with standard practice, once placed, AVGs should be used for hemodialysis access as soon as deemed appropriate by the nephrologist and/or operator. For standard ePTFE AVGs, the time from placement to first cannulation is typically after two weeks. Early cannulation AVGs can be used within one week after placement. Every effort should be made to minimize infection risk by removing central catheters as soon as possible.

11.0 FOLLOW-UP PROCEDURES AND GRAFT INTERVENTIONS

Subject Management
Prior to discharge, the study investigator or their designee should insure that the subject understands the postoperative care requirements, as determined by the physician, and the required follow-up schedule. The two-week visit should be scheduled.

It is recommended that investigators follow the *Fistula First Guidelines* for vascular access monitoring (http://esrdnetwork18.org/pdfs/QI%20-%20FF%20Tools/FFTool_VAMPFlowChrt.pdf or current).

Pharmacologic Regimen
There are no study-specific pharmacologic requirements. The need for intraoperative and postoperative anticoagulation therapy should be based on subject history and maintained as deemed appropriate by the physician. Anticoagulation/anti-platelet therapy will be recorded on the case report form (CRF).

Follow-up Evaluations
Subjects will be followed at two weeks and monthly thereafter through six months to assess AVG patency and complications. Measurement of access flow rate is part of standard care. Data from routine AV access flow monitoring performed as part of usual care, as available, will also be collected.

Graft ultrasound evaluation should be performed at the 3 month and 6 month follow-up visits and the results recorded on the CRF.

NOTE: For reference and in accordance with standard care, baseline flow measurements are typically assessed during 2 dialysis sessions 2 weeks apart; and monthly measurements will be performed thereafter. An access flow rate < 500 mL/min or a drop in access flow rate of 25% from baseline should trigger an angiographic evaluation of the AVG and possible intervention.

Telephone follow-up for subjects that miss the final (6 month) follow-up visit

If a study subject misses or is unavailable/unwilling to return for the final 6 month follow-up visit, telephone follow-up with the subject or their dialysis center should be attempted to determine the patency status of the AVG at 6 months (the primary study endpoint), and to gather as much additional information as possible in order to complete the 6 month follow up and study completion eCRFs. Telephone follow-up with subjects should be done only if the subject is unwilling or unable to come in. If the subject cannot be reached, then the dialysis center should be contacted (if allowed) in order to determine AVG patency at 6 months. If it is not possible to reach the subject by phone or to contact the dialysis center, then the subject will be considered as lost-to-follow up.

Post-procedure Graft Interventions

As per standard care following the AVG implant procedure, AVG interventions should be avoided within the first 7 days following the index AVG implant procedure. As warranted and determined by the physician, standard balloon angioplasty and thrombectomy procedures may be performed within the AVG, VIG, and adjacent native artery and vein. Mechanical thrombectomy devices that use spinning, rotating or other movable parts should NOT be used in the study, as this may result in entanglement or other damage to the VIG. The balloon diameter used should be equal to that of the VIG diameter and should be no larger than 6mm when used to treat the VIG segment that is within the AVG.

Summary of Tests and Procedures

The required schedule for subject treatment and follow-up evaluation is shown in **Table 1**.

Table 1: Schedule of Subject Treatment and Evaluation

Timeframe (window)	Test/Procedure
Pre-procedure (within 30 days)	Baseline imaging of target AVG site (performed as part of standard care) Baseline labs: Hgb, Hct, WBC, platelets
Pre-procedure (within 24 hours)	Urine pregnancy test for female subjects with reproductive potential
Immediately following end of AVG implant procedure (before leaving surgery suite)	Confirmation of AVG flow (e.g., palpable thrill, audible bruit. At the physician's discretion and if warranted, an angiogram may also be performed to confirm patency.
Post- procedure (within 48 hours)	Post procedure labs: Hgb, Hct
At discharge	Confirmation of AVG flow (palpable thrill, audible bruit)
2 weeks following the procedure (14 +4/-7 days)	Clinical follow- up with AVG evaluation (includes collection of information regarding any subsequent hospitalization, AEs, AVG interventions)
30, 60, 90, 120, 150,180 days following the procedure (± 14 days)	Clinical follow- up with AVG evaluation (includes collection of information regarding any subsequent hospitalization, AEs,

	AVG interventions) AVG flow rate evaluation (ultrasound or similar) is performed at the 90-day and 180-day follow-up visits.

Final Events
The following final events will justify cessation of study follow-up: death, AVG abandonment, lost to follow up (at least 3 attempts to contact the subject should be made and documented), or completion of study follow-up.

12.0 POTENTIAL RISKS

Potential adverse events that may occur and/or require treatment with use of the VIG include but are not limited to:

- allergic reaction to device materials or procedure medications
- anastomotic disruption or tearing
- aneurysm
- artery tear or rupture
- bleeding
- bruising
- contrast dye reaction
- death
- device breakage
- dissection or 'tissue flap' in blood vessels in which the VIG has been inserted
- embolism
- hematoma
- infection
- inflammation
- kinking/compression of the AVG and/or VIG device
- migration or misplacement of VIG device
- occlusion
- pseudoaneurysm in the AVG, VIG device, or adjacent native blood vessels
- seroma
- stenosis of the AVG
- swelling of implanted arm
- thrombosis of the AVG
- vessel spasm

Many of the potential adverse events listed above are similar to those that can occur during and after AVG placement using standard surgical techniques. Potential risks of a standard surgical procedure to implant an AVG for hemodialysis include but are not limited to the following:

- failure of sutures
- bleeding immediately after the procedure
- infection

- possible need for re-operation

The VIG will be used together with a standard 6mm AVG for hemodialysis that is sold and packaged separately. Potential adverse events that may occur with use of the AVG are described in the Instructions for Use packaged with the AVG.

Pregnant subjects are excluded from the study. In females of reproductive capacity, a pregnancy test must be performed prior to the procedure. This is to ensure that a fetus is not irradiated. Other potential risks to a fetus related to the study procedure are unknown.

There are no unique blood tests required for the study; however, results of standard blood tests performed to evaluate general health status at baseline, during the study procedure and during study follow-up will be included with the study data. Risks of having blood drawn include infection (rare) and bleeding (rare).

Steps to Minimize Risk
The following steps will be taken to minimize potential risks:

- Rigorous technical training will be provided to physician investigators that will perform the study procedures.
- On-site monitoring will occur during the first procedure at each site. On- site monitors will include a clinical representative of the sponsor. On-site monitors may also attend additional procedures throughout the course of the study.
- The study procedure will be performed in a surgical suite with radiologic imaging capabilities. In the event that the study procedure is unable to be performed (not expected), the patient will be able to receive traditional surgical graft implantation.

13.0 POTENTIAL BENEFITS

Potential clinical benefit(s) for the VIG are unknown at this time. Anastomoses with the VIG may potentially reduce venous vessel trauma, improve the local vessel wall shear stresses and promote laminar flow, thereby improving patency.

14.0 SUBJECT WITHDRAWAL FROM THE STUDY

Subjects may withdraw consent from the study at any time. Study data collected prior to withdrawal will be analyzed and included with the final study results. The investigator may withdraw the Subject from the study at any time if assessed to be in the best interest of the subject.

15.0 CRITERIA FOR STUDY TERMINATION

The study may be terminated at any time for reasons of safety, based on a recommendation by the IRB, the study DSMB, or based on other considerations by the Sponsor. Serious, device-related or possibly related adverse events that are unexpected in either frequency or type may prompt a review by the principal investigator, DSMB,

Medical Monitor and/or Sponsor, and may lead to consideration of stopping the study. Such a review and discussion will be documented and included with the study records.

16.0 STUDY DURATION

Enrollment is expected to occur over a 24-month period. The 6-month follow-up and 2-month period of data analysis and regulatory submission preparation is anticipated to be completed by Q2 of 2021.

17.0 TRAINING

The training of appropriate clinical site personnel will be the responsibility of Phraxis Clinical Department or their designees [e.g. Data Coordinating Center (DCC) staff]. To assure uniform data collection and protocol compliance, trainers will present a formal educational session to review the Investigational Plan, techniques for the identification of eligible subjects, instructions on data collection, follow-up schedules and regulatory requirements. Ongoing detailed email and telephone feedback regarding completion of CRFs will be provided by the DCC and through site monitoring to be performed by Phraxis representatives or their designee.

Prior to enrollment start, technical training on use of the study devices will be provided by a Sponsor representative, who may also attend/observe the roll-in cases. As part of the technical training, physician operators will also perform 'test deployments' of the study devices using a simulated-use model.

Roll-in Cases
Roll-in cases will be performed at each study site in order to confirm proper training and use of the study device and confirm comprehension of the study protocol. "Roll-in" subjects will be identified as such before enrollment and treated according to the same protocol and 6 month follow-up duration as used in the main study. Data from roll-in cases will be recorded using the same CRF as the main study. The number of roll-in cases per each site investigator will be determined by the Sponsor, in collaboration with the primary investigator at each site. No more than 1-2 roll-in cases per investigator are anticipated. The clinical experience and procedural data from roll-in cases will be reviewed by the Sponsor, in collaboration with each site investigator. Upon successful completion of the roll-in case requirements, as determined by the Sponsor, sites will be permitted to begin enrollment in the main study. Clinical data from roll-in cases will not be included in the primary study analysis but will be analyzed and provided in a separate clinical report at the end of the study. Data from roll-in cases will be included in the final safety analysis for the study.

18.0 STATISTICAL ANALYSIS

Analysis population
The primary analysis population will include all subjects enrolled since June 5, 2018 and treated with the VIG + sutured arterial anastomosis, and also all VIG sub-study subjects enrolled after October 17, 2017. Such subjects who meet the enrollment criteria and in whom use of the VIG is attempted will be included in the intention-to-treat primary analysis population.

Data from roll-in subjects or from subjects included in the interim analysis population will not be included in the primary study analyses but these data will be analyzed and summarized separately. This includes subjects who previously received an AIG.

Choice of Performance Goal

Based on a review of the literature, prior studies of AVGs cleared for commercial distribution, and on observations from the first 52 enrolled subjects that received an AIG+VIG (e.g., the interim analysis population), the observed cumulative patency rate at 6 months for standard AVG implants ranged from 65% to 98% (**Appendix B)**. Based on the proposed sample size for the current study (see below) and an expected cumulative patency rate of 84.6% for AVGs placed using the VIG, the exact, lower two-sided 95% confidence bound for cumulative patency is estimated to be 79.9%. A comparison to a target Performance Goal (PG) of 75% has been chosen for the evaluation.

Hypotheses

The primary study endpoint of the cumulative patency rate at 6 months will be evaluated in the following testable hypotheses:

H_0: $(\text{Cumulative Patency Rate})_{6\ \text{Months}} \leq PG$

H_1: $(\text{Cumulative Patency Rate})_{6\ \text{Months}} > PG$

where, PG = Performance Goal, here equal to 75%.

There are no formal hypotheses associated with the evaluation of secondary endpoints.

Data Analysis

General Statistical Considerations

a. Descriptive statistics will be used to summarize subject baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, medians, interquartile ranges, minimums and maximums. Categorical variables will be summarized in frequency distributions.
b. Statistical analyses will be performed by validated software (e.g., SAS, SPSS, or Cytel Software)
c. Copies of databases used to prepare clinical report summaries will be archived to enable any statistical analyses performed to be replicated.
d. A full data listing will be prepared, including an electronic version in a standard computer-accessible format (e.g., SAS) at the completion of the study. Listings of data represented on the CRF will be provided for all key baseline, demographic and outcome variables to facilitate further investigation of tabulated values and to allow for clinical review of safety variables.

A one-sided p-value of 0.025 will be considered evidence of statistical significance for the primary study endpoint.

Primary Endpoint

Cumulative patency at 6 months will be evaluated using the estimated patency from a Kaplan Meier survival analysis. The test statistic will take the following form:

$$\text{Z-test statistic} = (P - 0.75) / SE(P)$$

Where, (P) represents the Kaplan Meier estimate of cumulative patency at 6 months, and the standard error SE (P) is estimated using the method of Peto *et al (*1977*)*. [24]

Subjects who withdrawn for reasons other than loss of cumulative patency will be included in the analysis up until the time of withdrawal, and be considered censored in the analysis, according to usual convention, after withdrawal.

Secondary Endpoints

The following secondary endpoints will be evaluated in the study, but there are no formal hypotheses that are tested or associated significance levels assigned to results. Nominal confidence intervals may be calculated in summarizing clinical results for secondary endpoints but not for purposes of product labeling.

1. Acute device success will be summarized by the success rate and associated 95% confidence interval.
2. Primary Unassisted Patency at 6 Months will be summarized by the patency rate and associated 95% confidence interval.
3. Time-to-First-Cannulation will be summarized by the median time and frequency distribution.
4. Number and type of interventions required to maintain secondary patency will be summarized by the frequency distributions of numbers and types of interventions.
5. Number and type of serious adverse events (SAEs) will be summarized by frequency distributions of the numbers and types of SAEs, the subject rates of SAEs by type, and the proportion of subjects with at least one SAE.

Additional Safety Data

In addition to summarizing and reporting SAEs (Secondary Endpoint 5), the number and type of non-serious adverse events (AEs) will be summarized by frequency distributions of the numbers and types of AEs and the subject rates of AEs by type.

Gender Analysis

Cumulative patency rates between genders will be compared by gender using a log rank test statistic to compare their respective Kaplan-Meier survival curves. The heterogeneity of cumulative patency rates will also be examined using the test statistic used for the primary endpoint analysis. Gender specific summary statistics will also be provided for study primary and secondary endpoints.

Pooling of Sites

Cumulative patency rates will be compared between study sites using a Chi-square test to evaluate the association between rates and sites. A p-value of 0.15 or less will be considered evidence of a possible site interaction, requiring a further evaluation of subject baseline factors to determine if site differences can be explained by these factors.

Sample Size Justification and Planned Enrollment

Sample size adjustment recommendations from the planned interim analysis subject data have been considered in determining the sample size for the current study. The required sample size for the study was estimated using the following assumptions:

- Test basis: Kaplan-Meier estimate of cumulative patency rate at 6 months, with exact binomial estimation for purposes of sample size
- Type I error (alpha): 0.025 (one-sided)
- Statistical power: 80%
- Performance Goal (PG): 75%
- Expected cumulative patency for InterGraft at 6 months: 84.6%.

Based on the above assumptions, a total of 146 evaluable subjects will be required to compare observed cumulative patency to a PG of 75%. With an expected loss-to-follow-up rate of 8% over 6 months (e.g., 12 subjects), a total of 158 evaluable subjects will be enrolled into the main study, defined as primary analysis population of 146 subjects plus allowance for 12 subjects lost-to-follow up. Planned minimum and maximum enrollment under the current investigational plan is summarized in **Table 2**.

Table 2: Planned Enrollment in the Current Investigational Plan

Study Group	Minimum enrollment	Maximum enrollment
Roll-in	0	15
Primary analysis	146	146
Allowance for subjects lost-to- follow up	12	12
TOTAL	158	173

Planned enrollment under the entire study conducted under IDE G140221 is summarized in **Table 3**. This includes all subjects previously enrolled under the approved IDE G140221.

Table 3: Summary of Planned Enrollment under IDE G140221, as of May 22, 2019

Study Group	Maximum enrollment (or actual enrollment if known)
Roll-in subjects enrolled prior to May 22, 2019 (includes USA + Mexico Sites)	**25 (actual enrollment)**
Current Investigational Plan: Roll-in subjects	**up to 15**
Current Investigational Plan: subjects previous enrolled and to be included under the current investigational plan	**30 (actual enrollment)**
Current investigational plan: new subjects remaining to be enrolled after May 22, 2019 (Primary analysis + allowance for lost-to-follow up	**128**
Previously enrolled subjects that received VIG+ AIG (includes USA + Mexico sites, does not include roll-in cases)	**68 (actual enrollment)**
Previously enrolled subjects in VIG sub-study that are not included under the current Investigational Plan, but were included in the interim analysis)	**7 (actual enrollment)**
TOTAL	**273**

19.0 DATA REPORTING AND PROCESSING

Data Collection
Primary data collection based on source documented medical records will be performed by study coordinators or other designated research staff at each site. Electronic data capture (EDC) will be used. The EDC system(s) used will be compliant with FDA requirements. Site training on EDC data recording will be provided by the Data Coordinating Center (DCC). All EDC training will be documented in the Investigator site file. Throughout the study, a help desk at the DCC will be available for any questions that arise from the sites concerning EDC.

Notification of subject enrollment must be provided to the Sponsor within 24 hours. The enrollment notification may be made by email to the Sponsor or by entry of an enrollment form into the EDC within 24 hours of enrollment.

The following guidance is provided regarding entry of CRF data into the EDC:

- Pre-procedure (baseline) Imaging, Inclusion/Exclusion, Index Procedure, and Discharge information should be submitted within 2 days of enrollment.
- Follow-up Forms should be submitted within 2 days of the follow-up visit.

A complete copy of eCRF data to be collected is provided in **Appendix C**.

For any deaths that may occur throughout the study duration, efforts should be made to obtain a copy of the death certificate and autopsy report, as applicable.

Data Management
The DCC will use a validated clinical data management system consisting of a relational database and a web application to capture the study data through single-pass data entry. Automated edit checks for missing, discrepant, and out of range data will be programmed into the data entry forms, and manual edits will be conducted by the DCC Managers on an ongoing basis. The Sponsor will provide a list of edit checks to the DCC.

Any data discrepancies identified during data monitoring will be communicated to study sites for resolution or justification. Once all discrepancies and queries have been resolved, the site principal investigator will confirm the data accuracy with his/her signature on a Verification CRF. Once the study is completed, all data have been entered into the clinical database, and all discrepancies have been resolved, an audit will be conducted to verify that all requirements for database lock have been met. After database lock, the DCC will export the data into SAS datasets and provide them to the project statistician.

CRF submission status will be tracked by the Sponsor and DCC.

20.0 DATA MONITORING AND QUALITY ASSURANCE MEASURES

Sponsor Monitoring
Study site monitoring will be performed by Sponsor personnel or Sponsor designees (e.g. contract monitors). On-site monitoring will be performed to ensure that the study is conducted in compliance with applicable regulations

and with the study protocol. A pre-investigation visit will be made to each new study site to orient the staff to the study device and procedures, the study protocol, applicable regulations and requirements, study administration expectations. The prospective site will be evaluated to ensure that it has an adequate patient base and can provide sufficient staff and documentation support for proper study conduct.

No sites may receive shipment of study devices until the following documents are received by the sponsor:

- Written IRB approval for conduct of the study
- IRB approval of a consent form
- Signed Investigator Letter of Agreement
- Executed Study Agreement
- Copies of Investigator's CV and medical license
- Financial Disclosure

Clinical sites will be regularly monitored for timeliness and accuracy of data submitted to the DCC. Any evident patterns of noncompliance with respect to the protocol, data accuracy, maintenance of source documentation, or timeliness will be cause for the site to be put on probation. If correction actions are not made, the site will be asked to withdraw from the study.

Medical Monitor

An independent study medical monitor (MM) will be designated. The MM will be a qualified physician that is not a study investigator. The MM has the responsibility to review and evaluate information relevant to the study device safety throughout the development and implementation of the protocol. This oversight includes reviewing safety information and providing applicable recommendations to the sponsor. More specifically, the MM will:

- Evaluate all SAEs and review safety reports. SAEs will be evaluated immediately upon report of occurrence.
- Evaluate all UADEs at the time of occurrence.
- Advise the Sponsor (IDE holder)

Unanticipated Adverse Device Effects (UADE)

Federal law requires that the FDA be notified immediately of all Unanticipated Adverse Device Effects (UADE). Investigational device exemption (IDE) regulations define an UADE as "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 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" (21 CFR 812.3(s)."

The UADE review and notification process will be as follows:

(i) The study site will submit an Adverse Event (AE) report, indicating that the AE is serious and related or possibly related to the study device. Study sites must report all SAEs (including UADEs) to the Sponsor within 24 hours of discovery. If additional supporting information regarding the SAE is requested after the initial 24-hour report, the information will be promptly sent to the Sponsor, when available, via email.

(ii) The Sponsor will immediately conduct an evaluation and prepare a UADE report. The Sponsor will consult with the Medical Monitor (MM) as part of the UADE evaluation process, and the MM will review the UADE report and applicable information for clarity and completeness. The sponsor and MM may contact the site, as needed, for additional information and clarification.

(iii) The Sponsor will report the results of the UADE evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the Sponsor first receives notice of the UADE (§§ 812.46(b), 812.150(b)(1).

NOTE: Not all SAEs may bear a relation to the study device or procedure, and it is partly the responsibility of the MM to confirm that any claims of connectivity are reasonable and that all serious events are properly reported, regardless of causation.

In summary, the MM will collaborate with the Sponsor on safety oversight to meet human subjects' safety standards as defined by applicable Federal regulations, International Conference on Harmonization (ICH) Good Clinical Practice Guidelines (GCP).

Data and Safety Monitoring Board

An independent DSMB is established and has responsibility for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study. The DSMB is an independent group advisory to the Sponsor, and is required to provide recommendations about starting, continuing, and stopping the study. In addition, the DSMB is asked to make recommendations, as appropriate, to the Sponsor about:

- Efficacy of the study intervention
- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol and consent forms
- Performance of individual centers and core labs
- Participant safety, and
- Notification of and referral for abnormal findings

Details of DSMB operations are defined in the DSMB Charter document.

21.0 CLINICAL EVENTS

Adverse Event (AE) is defined as any undesirable sign, symptom or medical or psychological condition even if the event is not considered to be related or possibly related to the study device or study procedure/intervention. Medical condition/diseases present before starting the study will be considered adverse events only if they worsen after starting study treatment. An adverse event is also any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private

information under the research. Adverse events also include any problems associated with the use of a study device that adversely affects the rights, safety or welfare of subjects.

Serious Adverse Event (SAE) is defined as any undesirable sign, symptom, or medical condition which is fatal, is life-threatening, requires or prolongs in-patient hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital anomaly or birth defect, is medically significant and which the investigator regards as serious based on appropriate medical judgment. An important medical event is any AE that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions of SAEs.

Unanticipated Adverse Event (UAE) is defined as any event or experience that meets all three criteria below:

- Is unexpected in terms of nature, severity or frequency, given the research procedures that are described in the protocol-related documents AND in the characteristics of the subject population being studied
- Related or possibly related to participation in research. This means that there is a reasonable possibility that the incident may have been caused by the procedures involved in the research study.
- The incident suggests that the research placed the patient or others at greater risk of harm than was previously known or recognized OR results in actual harm to the patient or others

The occurrence of AEs, including SAEs and UAEs, will be monitored throughout the study duration. Adverse event information will be collected and reported on designated AE forms, assessed and classified by the principal investigator as serious/not serious. The investigator will also determine the relatedness of the AE to the study device and study procedure according to the following definitions:

- Related (AE is clearly related to the device/procedure);
- Possibly related (AE may be related to the device/procedure);
- Unrelated (AE is clearly not related to the device/procedure).

Procedure-related AEs are AEs that occur during the time interval from when the subject enters and leaves the surgical treatment suite for the index procedure (e.g., AVG implant procedure). Thus, the procedure includes use of the study device, as well as any treatments or procedures that are applied before or after the study device (eg, anesthesia, suturing of incision sites after AVG is completed), while the subject is in the surgical suite.

Device-related AEs are AEs related or possibly related to the study device or to the study device procedure which includes delivery, deployment, and attachment of the study device to the AVG.

Device-related events that occur during the study procedure are also procedure-related events.

Procedure-related events may not necessarily be related to the study device; for example, a procedure event such as an anesthesia reaction would not be related to the study device.

Device-related events may also occur after the study procedure, for example, fracture of metal strut in the VIG.

For situations in which a study subject has a serious adverse event (SAE) that results in abandonment of the study AV access site, the subject should be followed to the next follow-up visit after the study AVG is abandoned. This is done in order to collect general information about the subject's health status after the AVG is abandoned.

After that visit, the subject can then be formally withdrawn from the study. This means that the date that AVG patency is lost and the date of study withdrawal are not necessarily the same date.

Reporting and Review of Serious Adverse Events. SAEs must be reported to the Sponsor within 24 hours of discovery, and to national and local regulatory authorities, in accordance with national and local policies and procedures. In addition, all unanticipated adverse device effects (UADE) will be evaluated at the time of discovery and reported to the Sponsor within 24 hours. SAEs are reported by email or telephone call, using a designated SAE reporting form provided by the Sponsor.

A final determination as to whether an SAE meets the requirements for expedited reporting to the FDA and participating IRBs will be made by the study medical monitor and/or Sponsor.

Reporting Deaths.
Data regarding a subject death should be recorded on the AE/SAE eCRF as follows:
If the outcome of an AE is reported as FATAL, then the STOP DATE of the AE should be date of the death. The AE with the fatal outcome will generally be the 'cause of death' as stated in source documents. The AE causing the death should be recorded on the eCRF either by selecting from the checklist of specified AEs OR by selecting "Other" and then specifying the AE causing the death.

If a death is discovered during follow-up and there is no information available regarding the AE(s) leading to the death outcome, please complete the AE/SAE eCRF, and mark as "other" for AE type. Record 'fatal' for the outcome. The START DATE and STOP DATE recorded should be the same date, eg the date of death. In the "Event Summary" section, provide the date of death. Complete as much information as possible on this eCRF.

For all deaths, a copy of source document information (e.g., death record, hospital admission and discharge summary, etc) should be provided, if available. Deaths should be reported to the Sponsor within 24 hours of discovery, along with any available source documents describing the death, as available. Additional Source document information regarding the death, as may be requested by the study Clinical Events Committee or DSMB, should be provided as soon as it becomes available.

Clinical Events Committee
A Clinical Events Committee (CEC) will provide medical review of SAEs, UAEs, and any deaths that may occur throughout the study. The CEC will be comprised of the Medical Monitor, and the Sponsor's Chief Science Officer, Chief Technology Officer and Director of Clinical Affairs. Details of CEC operations are defined in a CEC Charter document.

The principal investigator/institution will permit study-related monitoring, audits of IRB/Ethics committee reviews, and regulatory inspections by providing direct access to source data and documents. On-site data monitoring will be performed by Sponsor's study monitors. Any data discrepancies will be resolved and documented by a standardized data query process.

22.0 PROTOCOL VIOLATIONS

Protocol Violation is defined as any change, deviation, or departure from the study design or procedures of the research project that is not approved by the IRB and study sponsor prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), national or local regulations. Protocol violations may or may not be under the control of the research team or hospital staff.

Major Protocol Violations
All major protocol violations must be reported to the IRB, as applicable and in accordance with local IRB policy, AND to the study sponsor, immediately upon discovering them, and no later than seven (7) calendar days from the time the study team receives knowledge of the event**.**

A major violation is a protocol violation that meets the following criteria:

- Represent a serious or continuing failure on the part of the study team to comply with the protocol, standard operating procedures, GCPs, federal, state or local regulations;
- Impacts subject safety or substantially alter risks to subjects. May or may not result in actual harm (clinical, emotional, social, financial, etc);
- Significantly damages the completeness, accuracy and reliability of the data collected for the study;
- Is under control of the investigator/research team/hospital staff.

Any evident patterns of noncompliance with the protocol requirements will be cause for the site to be put on probation for a period of 1 month. If corrective actions are not made, the site will be asked to withdraw from the study.

A log of all protocol deviations should be maintained in the study regulatory binder.

23.0 REGULATORY RESPONSIBILITIES AND CONSIDERATIONS

The responsibilities described in this section are required by Federal law and regulation (21 CFR 812, Investigation Device Exemptions; 21CFR 50, Protection of Human Subjects; 21 CFR 56, Institutional Review Boards).

Investigator Responsibilities
The study site investigator is responsible for ensuring that the study is conducted according to all signed agreements, the study protocol, and applicable FDA regulations. These responsibilities are listed below. In addition, each investigator must complete and sign the Investigator's Letter of Agreement provided by the Sponsor.

- IRB approval. The investigator must submit the study protocol to his/her IRB and obtain their written approval before being allowed to participate in the study. The investigator is also responsible for fulfilling any conditions of approval imposed by the IRB.
- Informed consent. Part of the IRB approval will include approval of Informed Consent text specific to the study. The investigator must administer the approved informed consent text to each prospective study subject, and obtain the subject's signature on the text, prior to study enrollment. A sample Informed

Consent form is included in **Appendix D**. This may be modified to suit the requirements of the individual site.

- Study coordinator. To assure proper execution of the protocol, site investigators must identify a study coordinator for the site. Working under the authority of the investigator, the coordinator will assure that study requirements are fulfilled, and will be the key contact person at the site for all aspects of study administration.
- Records. Site investigators must maintain accurate, complete, and current records relating to the conduct of the study. Such records include: key study related correspondence (e.g., correspondence with IRB, DCC, sponsor, study monitors); study device accountability records; subject case history information (CRFs, consent form, AE records).
- The study site principal investigator has overall responsibility for supervision of the use of the study device. The study investigator shall permit the device to be used only with subjects under his/her supervision.

- Reporting requirements. The investigator is responsible for reporting any unanticipated adverse device effects, SAEs, protocol violations, withdrawal of IRB approval, and other required reports (progress report and final report) according to the FDA guidelines and ICH GCP guidelines.

Sponsor Responsibilities

Phraxis, Inc. is the manufacturer of the VIG study device, the Sponsor of the study, and the IDE holder. The Sponsor's responsibilities include:

- Ensure that the study is conducted according to the signed study site clinical agreement, investigational plan and protocol, ICH GCP guidelines, and all applicable regulatory regulations.
- Provide study devices to participating study sites
- Provide study device training to investigators and study site staff
- Select the Principal investigator, site investigators, study sites and other study consultants (e.g. DCC) who participate in the study
- Provide financial support to study sites and consultants per individual Agreements
- Establish regulatory standards per federal regulations for clinical study sites and other study participants, and perform regular site monitoring to assure compliance with them.
- Perform site monitoring of clinical data at study sites

The Sponsor (Phraxis) retains ownership of all clinical data generated in the study and controls the use of the data for purposes of regulatory submission to the US and other governments.

<u>Supply of Study Devices</u>

VIG devices will be provided to each study site per the terms of a Study Agreement between Phraxis, Inc. and the site. At the cessation of the study, all unused study devices will be dispositioned per the agreements between the site and Phraxis, Inc.

Record Retention Policy

Study documents should be retained for at least two years after the last approval of a marketing application, and until there are no pending or contemplated marketing applications; OR at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will inform in writing

when study documents are no longer needed. Study sites should not destroy any study records without first confirming with the sponsor.

24.0 MEASURES TO AVOID BIAS

Measures that will be used to avoid bias include:

- Use of independent medical monitor and DSMB
- Use of independent statistician
- Objective criteria for endpoint determination
- Intention-to-treat primary analysis

25.0 PUBLICATION POLICY

The publication of results from any single center experience within the study is strongly discouraged until one year following the study's termination, in order to allow for preparation and publication of the multicenter results.

26.0 REFERENCES

1. U.S. Renal Data System. USRDS 2011 Annual Data Report: Volume 2. Atlas of End Stage Renal Disease in the United States. Bethesda, MD, National Institutes of Health, National Institutes of Diabetes, and Digestive and Kidney Diseases; 2011

2. www.fistulafirst.org/AboutAVFistulaFirst

3. Dember LM, Beck GJ, Allon M, et al. Effect of Clopidogrel on early failure of arteriovenous fistulas for hemodialysis: A randomized controlled trial. *JAMA* 2008; 299:2164-2171

4. Akoh JA. Prosthetic arteriovenous grafts for hemodialysis. *J Vasc Access* 2009; 10:137-147

5. Roy-Chaudhury P, Kelly BS, Zhang, et al. Hemodialysis vascular access dysfunction: From pathophysiology to novel therapies. *Blood Purif* 2003; 21:91-110

6. Lee T, Roy-Chaudhury P. Advances and new frontiers in the pathophysiology of venous neointimal hyperplasia and dialysis access stenosis. *Adv Chronic Kidney Dis* 2009; 16:329-338

7. Lok CE, Allon M, Moist L, et al. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM 1). *J Am Soc Nephrol* 2006; 17:3204-3212

8. Lee HW, Allon M. When should a subject receive an arteriovenous graft rather than a fistula? *Semin Dial* 2013; 26:6-10

9. Shingarev R, Maya ID, Barker-Finkel J, Allon M. Arteriovenous graft placement in predialysis subjects: A potential catheter sparing strategy. *J Kidney Dis* 2011; 58:243-247

10. Glickman MH, Stokes GK, Ross JR, et al. Multicenter evaluation of a polyurethaneurea vascular access graft as compared with the expanded polytetrafluoroethylene vascular access graft in hemodialysis applications. *J Vasc Surg* 200; 34:465-473

11. Hudson P. Early cannulation of vascular access sites for dialysis. *Dialysis and Transpl* 1996; 8:523-526

12. Roy-Chaudhury P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: A cellular and molecular viewpoint. *J Am Soc Nephrol* 2006; 17:1112-1127

13. NKF-KDOQI Clinical Practice Guidelines for Vascular Access: Update 2000. Part VI. Potential Quality of Care Standards, Guideline 30: Goals of Access Placement- Use of Catheters for Chronic Dialysis

14. Dixon BS, Beck GJ, Vasquez MA et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *NEJM* 2009; 360:2191-2201

15. Miller PE, Carlton D, Deierhoi MH et al. Natural history of arteriovenous grafts in hemodialysis subjects. *Am J Kidney Dis* 2000; 36: 68-74

16. Cinat ME, Hopkins J, SE Wilson. A prospective evaluation of PTFE graft patency and surveillance techniques in hemodialysis access. *Ann Vasc Surg* 1999; 13:191-198

17. Hurlbert SN, Mattos MA, Henretta JP et al. Long-term patency rates, complications and cost effectiveness of polytetrafluoroethylene (PTFE) grafts for hemodialysis access: a prospective study that compares Impra versus Gore-tex grafts. *Cardiovas Surg* 1998; 6:652-656

18. Bartlett ST, Schweitzer EJ, Roberts JE et al. Early experience with a new ePTFE vascular prosthesis for hemodialysis. *Am J Surg* 1995; 170:118-122

19. Hodges TC, Fillinger MF, Zwollak RM et al. Longitudinal analysis of dialysis access methods. *J Vasc Surg* 1997; 26: 1009-1019.

20. Evaluation of the GORE® ACUSEAL Vascular Graft for Hemodialysis Access. ClinicalTrials.gov identifier: NCT01173718 Results provided at: http://clinicaltrials.gov/show/NCT01173718

21. Data on file with Phraxis, Inc.

22. Yevzlin AS, Setum CM, Kallok MJ, Valliant A. Percutaneous AVG creation in a canine model. *Presented at the 2013 American Society of Diagnostic and Interventional Nephrology 9th Annual Scientific Meeting.*

23. Ebner, A, Ross JR, Setum CM, Kallok, MJ, Yevzlin AS. Transcatheter Anastomosis Connector System for Vascular Access Graft Placement: Results from a First-in-Human Pilot Study. *J Vasc Access* 2016; 17:111-117.

24. Peto R, Pike MC, Armitage P et al. Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of each Patient. *British J of Cancer* 1977; 35:1-39

25. Cui, L, Hung, HM, and Wang, SJ. Modification of Sample Size in Group Sequential Clinical Trials. *Biometrics* 1999; 55: 853-857