A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

CSP-1001

NCT03645681

Protocol V3 Approval Date: 22 May 2019

Amendment A Approval Date: 18 May 2020

Amendment B Approval Date: 18 December 2020

Informed Consent Approval Date: 02 March 2021

A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

Investigational Device: InnAVasc Vascular Access Graft

Protocol Number: CSP-1001

Version: 3.0, May 22, 2019

IDE Number: G180188

Sponsor

InnAVasc Medical, Inc.
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Durham, NC 27705 USA

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Revision History

Version 1.0 – 08 August 2018
Version 2.0 – 16 August 2018

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The sponsor or designee will maintain an updated list of principal investigators, investigation sites and institutions.

STATEMENT OF COMPLIANCE

This trial will be conducted in compliance with the protocol and the following regulatory requirements:

- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), E6 Good Clinical Practice: Consolidated Guidance (ICH E6(R2))
- ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- ICH E8 Guidance on General Considerations for Clinical Trials
- ISO14155:2011 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice
- Applicable sections of United States Food and Drug Administration (FDA) Code of Federal Regulations (CFR), including:
    - 21 CFR Part 50, Protection of Human Subjects
    - 21 CFR Part 54, Financial Disclosure by Clinical Investigators
    - 21 CFR Part 56, Institutional Review Boards
    - 21 CFR Part 812, Investigational Device Exemption Application
- Any other regional or national regulations, as applicable

Appropriate levels of clinical trial insurance will be obtained by InnAVasc Medical Inc.

PROTOCOL AGREEMENT

Investigator Name	**Title**
Site Name	**Site Number**

I have read the protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined therein.

I will provide copies of the protocol and all information on the device relating to past non-clinical and clinical experience, which were furnished to me by the Sponsor, to all physicians and other study personnel responsible to me who participate in this study and will discuss this material with them to ensure that they are fully informed regarding the device and the conduct of the study. I agree:

- To assume responsibility for the proper conduct of the study at this site, and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor, InnAVasc Medical, Incorporated (InnAVasc), or their authorized representatives.

- Not to implement any deviations from or changes to the protocol (including protocol amendments) without agreement from the sponsor and prior review and written approval from the Institutional Review Board (and FDA, if applicable) except where necessary to eliminate an immediate hazard to the subject(s), or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

- That I am familiar with the appropriate use of the investigational product, as described in this protocol and any other information provided by the sponsor including, but not limited to the current Investigator's Brochure or equivalent document provided by InnAVasc.

- To ensure that all persons assisting me with the study are adequately informed about the investigational product and of their study-related duties and functions.

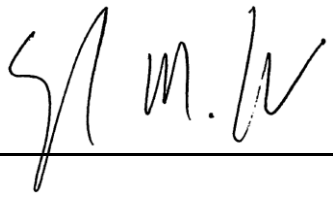
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the Investigational Product, and more generally about his/her financial ties with the sponsor. InnAVasc will use and disclose the information solely for the purpose of complying with regulatory requirements.

Investigator's Signature	Date

PROTOCOL APPROVAL

Sponsor Medical Approval: Shawn M. Gage, PA-C

Clinical Operations, Founder, InnAVasc Medical, Inc.

Signed:  Date: 22 May 2019

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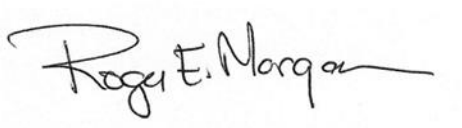
Signed:  Date: 22 May 2019

SYNOPSIS

Protocol Number:	CSP-1001
Investigational Device:	InnAVasc Arteriovenous Graft (InnAVasc AVG)
Study Title	A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease
Sponsor	InnAVasc Medical, Inc. 110 Swift Avenue Durham, NC 27705 USA
Study Objective	To evaluate the safety and effectiveness of the InnAVasc Arteriovenous Graft for hemodialysis access in patients with end-stage renal disease (ESRD).
Intervention Description	Patients will be implanted with an InnAVasc AVG in the forearm or upper arm using standard vascular surgical techniques. The graft will be placed in a "straight" (soft "C") configuration in the upper arm, or looped configuration in the forearm (forearm loop) or upper arm (axillary loop). Placing the graft across the elbow will be prohibited.
Subject Population	Patients with ESRD who require hemodialysis and are suitable for an AVG for hemodialysis access will be eligible for inclusion in the study.
Subject Sample size	60 subjects will be treated in the study
Number of Sites	Up to 10 investigational sites in the United States
Study Design	Prospective, multi-center, single arm, non-randomized study
Expected Enrollment Start	Q4 2018
Estimated Accrual Period	Approximately 9 months
Study Duration and Consent	**Regulatory trial duration** The primary endpoint of secondary patency will be assessed at 6 months, but follow up will continue out to 2 years. The 510(k) will be submitted when the final subject completes their 6-month follow-up. **Overall trial duration** Subjects will be followed up for 24 months. The total expected duration of the clinical investigation for each subject is 25.5 months.

Primary Effectiveness Endpoint	Secondary patency at 6 months. • Secondary patency is defined as the time from placement of the AVG to abandonment, including surgical or endovascular interventions designed to reestablish AVG patency.
Primary Safety Endpoint	Incidence of adverse events of special interest (AESIs) through 6 months, defined as: 1. Infection of the study device; 2. Pseudoaneurysm formation at any point along the access circuit requiring surgical/endovascular intervention, including thrombin injection and compression (pseudoaneurysms that occur at sites of needle cannulation, but which are small enough to be observed without intervention, do not trigger this element of the AESI endpoint); 3. Bleeding from the access circuit requiring surgical/endovascular intervention or ≥2-unit blood transfusion; 4. Hematoma from the study device requiring intervention; 5. Seroma of the study device requiring intervention. 6. Thrombosis of the study device.
Secondary Endpoints	1. Functional patency at 3, 6, 12, 18 and 24 months; 2. Time to successful cannulation, defined as the time from the index procedure to the first 2-needle dialysis session through the study device; 3. Proportion achieving sustained use of 3 months, 6, months, 12 months, 18 months, and 24 months. Sustained use is a period of time in which the study graft is used for consecutive dialysis sessions without the requirement for alternative hemodialysis vascular access to allow for renal replacement therapy. A sustained use period can be achieved at any time throughout the study period of 24 months.
Exploratory Endpoints	Unless otherwise specified, all exploratory endpoints will be assessed at 3, 6, 12, 18 and 24 months 1. Primary patency rate; 2. Assisted primary patency rate; 3. Days of central venous catheter in situ; 4. Incidence of individual adverse events;

	5. Change from baseline Patient Reported Outcomes Measures/Patient Reported Experience Measures (PROM/PREM) survey; 6. Health economics derived from collected study data, e.g.
	a. Overall cost to create and maintain arteriovenous (AV) access b. Catheter related costs c. Cost of AV access related complications
Inclusion Criteria	**Patients must meet the following criteria to be included in the study:** 1. Patients with ESRD who are not, or who are no longer, candidates for creation of an autologous AV fistula and therefore need placement of an AV graft to start or maintain hemodialysis therapy; 2. Age 18 to 80 years old, inclusive; 3. Suitable anatomy for implantation of upper arm "straight" or looped graft, or forearm looped graft (graft not to cross the bend of the elbow); 4. For patients NOT on Coumadin / warfarin, international normalized ratio (INR) ≤1.5; 5. Able and willing to give informed consent; 6. Anticipated life expectancy of at least 1 year. **Additional inclusion criteria on Day 0 (intraoperative):** 7. Both vessels have been exposed and are deemed appropriate for implantation (i.e. based on the surgeon's opinion, artery is of adequate size, has adequate pulse to support AV access flow and is safely clampable (i.e. artery has lack of significant calcification); and the vein is of adequate size, free of localized sclerosis, and is free of immediate outflow obstruction).
Exclusion Criteria:	**Patients will be excluded from the study for:** 1. History or evidence of severe cardiac disease (New York Heart Association [NYHA] Functional Class III or IV), myocardial infarction within 6 months prior to enrollment, ventricular tachyarrhythmias requiring continuing treatment, or unstable angina; 2. Diabetes with a hemoglobin A1c (HbA1c) > 10% 3. For upper arm straight configuration, antecubital

	fossa crease to axillary crease distance < 18 cm. 4. History or evidence of severe peripheral arterial disease in the extremity selected for implant (i.e. arterial inflow insufficient to support hemodialysis access); 5. Known or suspected central vein stenosis or obstruction on the side of planned graft implantation; 6. In the opinion of the investigator, baseline hypotension, or history of frequent hypotensive episodes during dialysis that puts the patient at increased risk of graft thrombosis; 7. In the opinion of the investigator, uncontrolled hypertension; 8. Baseline hemoglobin <8 g/dL; 9. Baseline platelet count <100,000 or >500,000 cells/mm^3; 10. Documented history of stroke within 6 months prior to enrollment; 11. Treatment with any investigational drug or device within 30 days prior to enrollment; 12. Female patients who are pregnant, intending to become pregnant, nursing or intending to breastfeed during the study (pregnancy test may only be omitted, if patient is post-menopausal or has a documented history of hysterectomy); 13. History of cancer with active disease or treatment within the previous year, except for non-invasive basal or squamous cell carcinoma of the skin; 14. Immunodeficiency, including documented history of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) or patients receiving immunosuppressive therapy for treatment of an acute inflammatory event or autoimmune flare. Chronic immunosuppressive therapy is acceptable; 15. Documented or suspected hypercoagulable state; 16. Bleeding diathesis, other than that associated with ESRD; 17. Documented history of heparin-induced thrombocytopenia (HIT); 18. Active local or systemic infection as documented

	from the medical history or bloodwork / blood culture data. If the infection resolves, the subject must be at least one-week post resolution of that infection before implantation; 19. Scheduled renal transplant within 6 months; 20. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and effectiveness of the InnAVasc AVG.
Primary Analysis Population	The primary analysis population is the intention to treat (ITT) cohort which is defined as the subjects in whom the host vessels have been deemed appropriate by the investigator for placement of an AVG and the investigator has made the decision to proceed with implantation of the investigational device.
Statistical Analyses	Primary safety and effectiveness endpoints will be summarized via standard descriptive statistics, including exact binomial 95% lower confidence intervals for dichotomous variables. No hypothesis tests are planned and there are no *a priori* study success criteria specified.
Sample Size Calculation	A sample size of 60 subjects will provide: • A sufficiently precise 95% lower bound on the secondary patency rate at 6 months, and • Working cohort to enable capture of the adverse event profile associated with the use of the InnAVasc Vascular Access Graft.
Baseline Testing	Medical history, physical examination with vital signs, laboratory assessment, and mapping of vessels to ensure suitability of the implantation site and to exclude suspected central vein stenosis on the side of graft implantation.

Follow-Up Schedule	Subjects will have required in-person follow-up evaluations at the following time points post index procedure: 1. 14 days; 2. 45 days; 3. 6 months; 4. 12 months; 5. 24 months Subjects will have required telephone check-up/dialysis clinic contact evaluations at the following time points post index procedure: 1. 1 month; 2. 3 months; 3. 4 months; 4. 5 months 5. 9 months 6. 18 months
Timing	The data will be analyzed and submitted for 510(k) clearance when the last subject completes their 6-month follow-up. Additional 24-month data will be analyzed for safety.
Data Safety Monitoring Board (DSMB)	An independent DSMB will review safety data from the study at predetermined time points and as deemed necessary by the Sponsor or the DSMB Chair. The DSMB will make recommendations on protocol modifications and continuation of the study.
Protocol Version and Date	Version 3.0; 22 May 2019

ABBREVIATIONS

ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired Immunodeficiency Syndrome
AV	Arteriovenous
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
CBC	Complete blood count
CDC	US Centers for Disease Control and Prevention
CKD	Chronic kidney disease
CRF	Case Report Form
CRO	Contract Research Organization
CVC	Central venous catheter
DSMB	Data and Safety Monitoring Board
eCRF	Electronic case report form
EDC	Electronic data capture
EPPY	Events per patient year
ePTFE	Expanded polytetrafluoroethylene
ESRD	End stage renal disease
ET	Early termination
FDA	US Food and Drug Administration
HbA1c	Hemoglobin A1c
HD	Hemodialysis
HIV	Human Immunodeficiency Virus
HIT	Heparin induced thrombocytopenia
IB	Investigator brochure
ID	Individual identification

IFU	Instructions for Use
InnAVasc AVG	InnAVasc arteriovenous graft
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention to Treat
LSR	Liquid silicone rubber
NYHA	New York Heart Association
PA	Pseudoaneurysm
PASS	Power analysis and sample size
PREM	Patient reported experience measures
PROM	Patient reported outcome measures
SADE	Serious Adverse Device Effect
SAF	Safety Analysis Set
SIV	Site initiation visit
SOP	Standard Operating Procedure
TMF	Trial master file
USADE	Unanticipated Severe Adverse Device Effect
USRDS	United States Renal Data System

1 INTRODUCTION AND BACKGROUND

Chronic kidney disease (CKD) is a worldwide health problem, with a global prevalence of between 11-13% of the adult population.[1] A recent report from the United States Renal Data System (USRDS) estimates the prevalence of CKD to be 14.8% in the U.S. alone.[2] The prevalence of CKD is rising in tandem with the increased prevalence of its risk factors, such as older age, diabetes mellitus, hypertension, cardiovascular disease, and obesity.[1,3] Patients with CKD can progress to end stage renal disease (ESRD) and require long-term hemodialysis (HD) or kidney transplantation. Patients with diabetes mellitus or hypertension tend to progress to ESRD faster than patients with other comorbid conditions,[4] therefore, as these conditions are increasing in prevalence, the number of patients with ESRD is also expected to increase. Worldwide projections show the number of patients with ESRD is increasing, especially in developing countries.[5] A recent report shows that there are nearly 700,000 cases of ESRD in the U.S., a number that has increased by approximately 100,000 since 2012.[2,6] An increase in the number of patients with CKD and ESRD signifies an increasing financial burden. The total Medicare spending on both CKD and ESRD was over $50 billion for people aged over 65 years, or approximately 20% of the overall Medicare spending in that age group in 2015,[2] and these costs are projected to rise.

For patients with ESRD, HD is a vital therapy. Needle access to a surgically created, high flow, vascular shunt or arteriovenous (AV) access is required 3-5 times a week. It is imperative that the AV access is efficient and well performing for HD therapy to be effective. Complications relating to AV access, such as infections and thrombosis, are the main reason for morbidity among HD patients.[7] The ideal AV access should be easy to place, available for immediate use, low cost, able to provide proper blood flow, long-lasting, and without complications.[8,9] There are 3 main types of AV accesses available for HD: a central venous catheter (CVC), an AV fistula (AVF), or an arteriovenous graft (AVG). However, new innovations in AV access technology are necessary, as none of the current AV access modalities are ideal and there are advantages and disadvantages with each of these forms of AV access.

Of the three types of AV access, CVCs are not recommended for long-term AV access.[9,10] However, as other forms of AV access need time to mature, HD is often initiated with a CVC.[11] When another AV access site fails, or in an emergency situation, CVCs provide immediate vascular access, often via the right internal jugular vein.[12,13] However, CVCs are not recommended for long term use as they are associated with an increased risk of infection, poor blood flow, and shorter HD duration.[7,11,14,15] Therefore, other forms of AV access are required to maintain HD long-term.

The AVF is the most common form of vascular access and is usually the first choice for treatment.[11,16] An AVF is created by surgically joining an artery to a vein, usually the brachial or radial artery to the cephalic or basilic vein.[9] The AVF results in arterial blood flowing directly into the vein, causing engorgement and thickening of the vein. The AVF can be used when it is considered mature, which can take weeks for the adequate dilatation and thickening of the vessel wall that is required for successful cannulation. This delay can

require patients to rely on the use of CVCs for HD access. Overall, the AVF is generally considered to be highly effective, with a low rate of complications and a lower cost compared to other forms of AV access.[9,10,16,17] Patients with AVFs have better outcomes compared to those with other forms of vascular access.[11] Old age, peripheral vascular disease, diabetes mellitus and hypertension are the main risk factors for AVF failure.[18] These comorbidities can affect the quality of the vascular bed, leading to endothelial dysfunction, and impaired dilation which can increase the likelihood of neointimal hyperplasia and stenosis.[18-20] However, not all patients are suitable for treatment with an AVF. Early thrombosis (< 6 weeks after placement) and inadequate maturation are the main reasons for failure of AVFs.[9,10,18] In these cases, an open surgical or, more often, an endovascular intervention is required to rescue the AVF. In some cases, a new vascular access may be required. These reinterventions and reoperations add significantly to the cost of AVF and the lower the chances of maintaining vascular access over the long-term.

In situations where the construction of an AVF is not suitable or cannot be used, AVGs often provide a viable alternative.[11] AVGs may be appropriate in high-risk patients, late referred patients, elderly patients, patients with severe comorbidity burden or patients with a history of recurrent AVF failure. The use of expanded polytetrafluoroethylene (ePTFE) was introduced as a suitable prosthetic graft for vascular access in the 1970s,[21] and it is now commonly used for connecting arteries and veins. The AVG is often placed between the brachial artery to the axillary vein in a straight configuration in the upper arm or a looped configuration between the brachial artery and cephalic or brachial/basilic vein in the forearm.[9] Grafts constructed from ePTFE require prolonged periods of healing until the time of safe cannulation, to allow tissue incorporation. This period can take 2 to 5 weeks[8], requiring patients to rely on the use of an external dialysis catheter for HD access. These catheters, which serve as a direct line from the outside of the body to the blood stream, place the patient at significant risk for a blood stream infection, sepsis, and death. [7,11,14,15] This period is shorter than the maturation time for AVF, but still not ideal. However, there are some newer AVGs that allow for faster cannulation.[22,23] Unlike AVFs, blood flow through an AVG is dependent on the size of the graft, and not the maturation of vessel. Therefore with a prosthetic graft there is a better chance of achieving adequate blood flow.[10,24] Also, AVGs, are easier to cannulate, with a larger area for cannulation, they offer more cannulation sites.[24]

However, AVGs have disadvantages and many complications can occur. AVGs are associated with a risk of infection, aneurysm formation, stenosis, thrombosis, and degradation of the graft material.[19,25-27] Some of these complications result from improper graft puncture technique and repeated trauma due to needle cannulation. Needle punctures of the graft wall can damage the graft material lead and to the formation of hematomas and pseudoaneurysms (PAs).[28,29] Graft degradation can be significantly accelerated by inadvertent puncture of the posterior or sidewall of the graft. The growth of hematomas can result in thinning and erosion of the skin, leading to a risk of bleeding, thrombosis and ultimately surgical intervention.[27] Overly aggressive graft compression, in an attempt to provide hemostasis following needle withdrawal, can also result in graft thrombosis and

failure. Infections are another major complication associated with AVGs, often as a result of frequent cannulations, which can introduce an infection around the access site.[27,28] These complications have serious side effects, resulting in bleeding, pain, disability and ultimately surgical interventions, which if unsuccessful can lead to abandonment and explantation of the graft.[27,29] Largely due to these complications, AVGs generally have a shorter lifespan than AVFs (< 2 years compared to < 5 years).[30,31]

The devices and equipment used in AV access have improved in the last decade, however, there is still room for improvement as many complications persist. Surgical and endovascular interventions to manage these complications can lead to huge healthcare expenditures annually. Therefore, innovations that can prolong the survival of the AVG and reduce or prevent complications associated with AVGs are a necessity.

1.1 Scientific Rationale

Currently, no available grafts offer protection from needle access injury, and no United States Food and Drug Administration (FDA)- approved HD grafts offer immediate cannulation. Only 2 grafts are FDA cleared for early access (24-72 hours post implant [Vectra, CR Bard, and Acuseal, W.L. Gore]), but outcomes data for these devices are lacking. To mitigate dialysis access graft cannulation complications, InnAVasc has developed an AVG modification that incorporates two multilayer cannulation chambers with potentially improved low bleed technology that are resistant to posterior and sidewall needle penetration/injury; the InnAVasc arteriovenous graft (InnAVasc AVG). This device has the potential to eliminate many of the current complications and costs associated with AVG failure and infection, and thus could relieve patient-associated pain and suffering, as would potentially lead to a significant reduction in health care costs related to chronic dialysis graft injury.

1.2 Potential Risks and Benefits

1.2.1 Potential Risks

It is anticipated that subjects participating in the study will be exposed to the same risks as those associated with other AV grafts. Risks associated with the study device may include but are not limited to:

- Bleeding and hematoma formation at the surgical site or the dialysis puncture sites
- Thrombosis/occlusion of the graft or host vessels
- Infection of the graft, at the surgical site or systemically
- Skin erosion
- Steal syndrome
- Stenosis of the graft or its anastomoses

- Swelling of the limb

Regular clinical examination of the graft site and assessment of the graft patency and blood flow using ultrasound during the study should allow early detection of graft complications and permit appropriate intervention including graft explantation if necessary.

1.2.2 Potential Benefits

Subjects who undergo implantation of the InnAVasc AVG may benefit from immediate and improved reliable hemodialysis access versus the challenges posed by a conventional ePTFE graft. In addition, the risks listed in Section 1.2.1, most importantly bleeding and hematoma formation, typically encountered with conventional ePTFE grafts may be decreased with the InnAVasc AVG. Finally, the longevity of the InnAVasc AVG may be greater than that of conventional ePTFE grafts.

1.2.3 Risk-Benefit Rationale

As mentioned above, subjects who undergo implantation of the InnAVasc AVG may benefit from immediate and improved reliable hemodialysis access versus a conventional ePTFE graft. The risks anticipated in this study are similar to those associated with currently marketed prosthetic grafts used for dialysis access. The superficial site of implantation of the InnAVasc AVG, when used for dialysis access, facilitates clinical and regular ultrasound monitoring of the graft, allowing any such complication to be recognized and treated promptly, thus minimizing potential risk to the patient. The potential advantages of the InnAVasc AVG compared to currently marketed grafts may lead to a lower complication rate and reduced need for surgical intervention.

To summarize, unique potential benefits of the investigational device include, early use (same day as implant), reduced dialysis catheter contact time for the patient, reduced infections, significantly reduced bleeding following needle removal (self-sealing potential) [patient safety], less dialysis chair time [patient/technician convenience], easy identification of the cannulation area [enhancement for dialysis technicians/patient safety], reduced pain/suffering for patient, and protection from commonly suffered graft back and side wall needle injuries during the cannulation process [enhanced safety for the patient, reduced hospitalizations and interventions]. Furthermore, this device is intended for use in patients with end stage renal disease who require hemodialysis. By definition, ALL patients who receive this device will be Medicare beneficiaries as long as they have required renal replacement therapy for greater than 90 days, and therefore ALL patients who benefit from the enhanced features of this investigational device will be Medicare beneficiaries.

2 INVESTIGATIONAL DEVICE

2.1 Overview

The Sponsor, InnAVasc, (Durham, NC), has developed the study device known as the InnAVasc AVG. The InnAVasc AVG is a hemodialysis vascular access graft, intended for implantation in the lower or upper arm using standard vascular techniques, in patients requiring hemodialysis.

2.2 Manufacturer

Manufactured by:

Medical Murray
4508 Westinghouse Blvd. Suite B
Charlotte, NC 28273 USA
Ph: +1 847.620.7990
Fax: +1 847.620.7995
ncinfo@medicalmurray.com

For:

InnAVasc Medical, Inc.
110 Swift Avenue
Durham, NC 27705 USA

2.3 Model Numbers

The InnAVasc AVG will be made available in two models for the clinical study (Straight, model #017717 and Looped, model #023000).

2.4 Device Traceability

Lot numbers will be used to trace devices used in the study. A unique lot number will be assigned to each device.

2.5 Intended Purpose of the Investigational Device in the Clinical Investigation

The investigational device is a sterilized, single-use implant intended for use as a vascular prosthesis (blood access for hemodialysis) as an implanted vascular access conduit for hemodialysis. It will be surgically implanted in the forearm or upper arm. The first end of the graft is connected to an artery and the second end is connected to a vein, such that blood flows through the conduit from artery to vein. Implantation of the graft will occur once and the graft will be accessed by needle cannulation, on average, 3 to 5 times per week.

2.6 Indications for Use

The InnAVasc AVG is intended for use in hemodialysis patients who are not candidates for the creation of an autologous AV fistula.

2.7 Device Description

The InnAVasc AVG is a modified graft technology, aimed at improving AVG safety and access, in patients with ESRD requiring hemodialysis. As currently designed, the InnAVasc AVG makes no changes to the construction of a standard 6 mm ePTFE vascular graft, but rather incorporates added safety features such as semi-rigid, penetration-resistant cannulation chambers that have been externally molded and bonded to one contiguous segment of vascular graft tubing. The modified design of the InnAVasc AVG allows for continuous flow, and immediate, durable and easier cannulation. The looped and straight configurations undergo the same manufacturing process. The only difference between the two models is the distance between the two chambers (closer for straight, further apart for looped) to allow the necessary differences in tunneling geometry.

The InnAVasc AVG is constructed of biocompatible material and has one continuous lumen that is designed to allow for uninterrupted blood flow, as there are no transition points. The device has a semi-rigid design, which reduces graft compression and expansion, thereby minimizing disruptions in blood flow. A thin (0.15 mm) ePTFE veneer covers the cannulation chamber to create a graft surface with continuous ePTFE coverage. This external finish is crucial to promote tissue ingrowth and incorporation across the entire graft for purposes of stability.

Another advantage of the InnAVasc AVG is that it should be able to be used immediately post implantation. The device contains two specialized cannulation zones. The liquid silicone rubber (LSR) material used in these zones is self-sealing, allowing for early cannulation. The LSR material is on the external surface of the graft, so as not to interrupt blood flow. The back plate of the cannulation zone is constructed of medical grade polysulfone, which is a strong, stable, biocompatible material, that is resistant to inadvertent needle puncture. Due to the specialized cannulation area, the AVG has the potential to be easily cannulated even by inexperienced users.

Overall, this device has the potential to reduce many of the complications associated with AV grafts, such as, graft injury due to improper cannulation, graft compression and low blood flow. In addition, a major advantage of this AVG is that we postulate that it can be cannulated immediately after implantation, therefore the implantation of temporary a CVC is not necessary, reducing the risk of infections and CVC- associated complications.

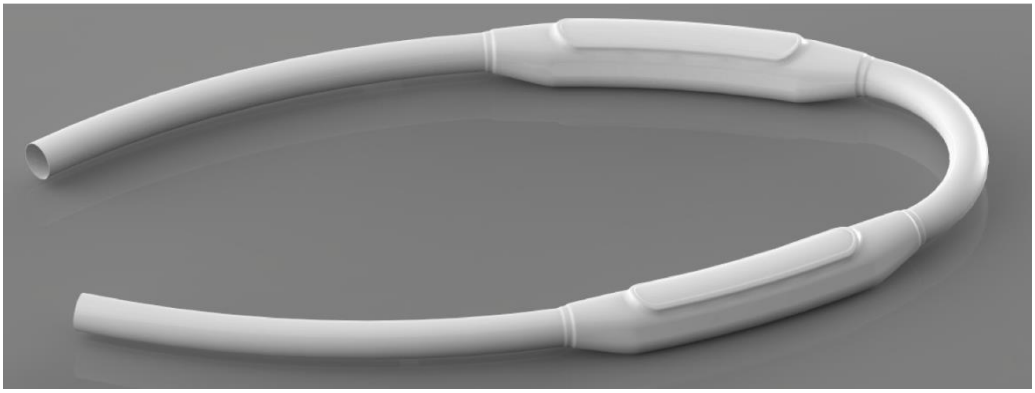


Figure 1: *InnAVasc Arteriovenous Graft (Looped Configuration shown)*

A cross section of the InnAVasc Graft is provided in Figure 2 (clear area consists of silicone).

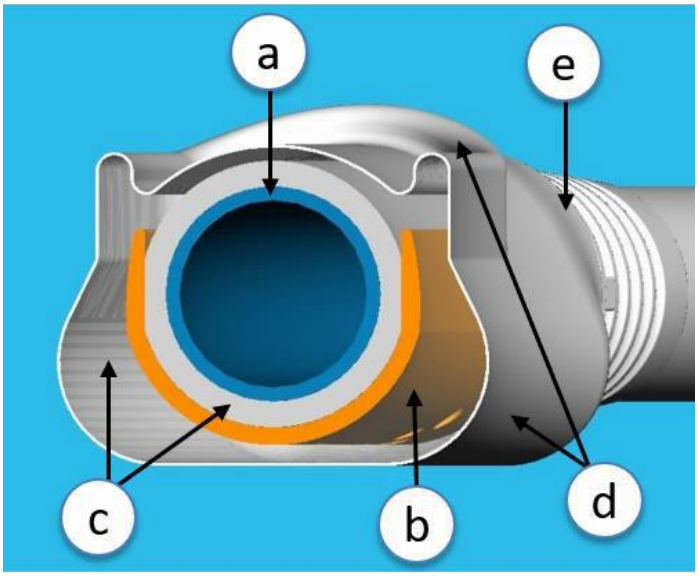


Figure 2: *Cross section of InnAVasc Arteriovenous Graft. InnAVasc components are labeled in Figure 2 above: a) base graft (CR Bard Impra AVG, K830543), b) polysulfone back plate, c) silicon molding, d) ePTFE sleeve, e) ePTFE tape.*

2.8 Implantation of the InnAVasc AVG

The InnAVasc AVG is implanted using standard vascular surgical techniques similar to placement of predicate peripheral vascular prostheses. Implantation of the InnAVasc AVG will be undertaken by qualified vascular surgeons experienced in dialysis access surgery. The InnAVasc AVG is tunneled in the subcutaneous space using a standard Kelly-Wick tunneler using a 10 mm tunneling tip for the initial tunnel. The graft is attached to the tunneling rod using a 6 mm tunneling tip to be pulled back through the subcutaneous tissue. For straight configurations, ensure that the natural curvature of the graft is positioned such that the arc is lateral on the extremity. For looped configurations, ensure that the natural curvature of the chambers and graft conform to a loop (arc of lateral chamber points lateral, arc of medial chamber points medial). The blue stripe on the graft and the palpable cannulation ovals must be oriented anteriorly. For straight configurations, it is recommended to pull the graft from the arterial exposure site towards the venous exposure site when possible to avoid stretching the arterial limb of the graft. Stretching the arterial limb of the ePTFE can increase the risk of graft ultrafiltration syndrome ("weeping syndrome"). For looped configurations, it is recommended to pull each limb, separately, through the counter incision, toward the vascular exposure site. The anastomoses are fashioned using 5-0 or 6-0 polypropylene suture with a running or interrupted technique. Intraoperative anticoagulation is used at the investigators' discretion.

2.9 Use of the InnAVasc AVG for Hemodialysis

The InnAVasc AVG is accessed for hemodialysis in the same fashion as standard dialysis grafts, using two hemodialysis needles; one for arterial draw to the dialysis machine, and the other for venous return to the subject. The InnAVasc AVG has two cannulation chambers (one arterial, one venous) in which one standard dialysis needle (15, 16, or17 gauge) is placed in each chamber to commence HD. It is recommended to use the smallest bore needle to provide the prescribed hemodialysis over the prescribed time. Each cannulation chamber can be easily identified by the palpable cannulation oval on the anterior chamber. The needle should penetrate the chamber on or within the cannulation oval at a 45-degree angle for best results. It is recommended to keep the needle tip within the lumen of the graft, but if the tip advances beyond, the safety backplate will prevent the needle from penetrating the posterior or side walls of the graft. Due to the firmness of the chamber, it may be best to stabilize the needle at the cannulation angle and secure rather than securing the needle flat to the subject's arm. At the conclusion of HD, mild to moderate digital pressure should be applied to the puncture site for 30-60 seconds before applying a small bandage. Pressure dressings are not required for the InnAVasc AVG. The design of the InnAVasc AVG is such that it can be cannulated and used for HD on the same day as surgical implant. The self-sealing technology, combined with the safety backplate will prevent backwall injuries and/or bleeding of the puncture site into the peri-graft space, which can lead to graft thrombosis, subject hemorrhage, and infection. Subjects will be asked to wear a study ID band for purposes of identification for the study, but also to provide cannulation instructions via a linked QR code printed on the band. This is in addition to education provided first hand from the dialysis organizations directly to the dialysis units and additional education provided

directly from the Sponsor. **For purposes of this clinical investigation, the expectation is that the first use of the InnAVasc AVG for two needle HD will occur on the same day as implant, or the next day, but not beyond 7 days post implant as long as medically appropriate.**

3 SUMMARY OF PRE-CLINICAL STUDIES AND PRIOR CLINICAL INVESTIGATIONS

The non-clinical testing program was designed to evaluate the InnAVasc AVG's ability to function *in vivo* as intended as a hemodialysis graft and to address post cannulation time to hemostasis, hematoma formation, prevention of posterior wall penetration, ease of access, and graft patency. Overall, the results of these studies indicated that the InnAVasc AVG was substantially equivalent or superior to the control (standard ePTFE) in all addressed aspects. Generally, the grafts functioned as intended and maintained patency, or assisted patency during the study period. A detailed description of these studies, including bench testing, are outlined in the Investigator Brochure (IB).

This clinical investigation will be the first evaluation of the InnAVasc AVG in humans and will allow the Sponsor to collect safety and effectiveness data regarding its device.

4 STUDY OBJECTIVE

The objective of this study is to evaluate the safety and effectiveness of the InnAVasc AVG for hemodialysis access in patients with ESRD. The safety and the effectiveness of the device and the procedure will be assessed using separate primary endpoints through 6 months.

5 STUDY DESIGN

The study population will include up to 60 subjects, male and female, who are appropriate candidates for implantation of an InnAVasc AVG and require hemodialysis treatment for ESRD.

5.1 Study Design

This clinical trial is a prospective, multi-center, single-arm, non-randomized, premarket study designed to assess the safety and effectiveness of the InnAVasc AVG device in subjects with ERSD who require HD. The safety and effectiveness of the device will be evaluated with primary safety and effectiveness endpoints that will be summarized via standard descriptive statistics, including exact binomial 95% lower confidence intervals. No hypothesis tests are planned and there are no *a priori* study success criteria specified.

Data will be collected through 24 months.

5.2 Informed Consent

Written, study-specific informed consent will be obtained from each subject prior to the first study-specific procedure. The investigator will keep the original informed consent form and a copy will be given to the subject. It will also be explained to the subjects that they are free to take part in the study and free to withdraw from the study at any time without prejudice to future treatment. A subject is considered enrolled after informed consent has been completed.

5.3 Inclusion Criteria

Patients must meet the following criteria to be included in the study:

1. Patients with ESRD who are not, or who are no longer, candidates for creation of an autologous AV fistula and therefore need placement of an AV graft to start or maintain hemodialysis therapy;
2. Age 18 to 80 years old, inclusive;
3. Suitable anatomy for implantation of upper arm “straight” or looped graft, or forearm looped graft (graft not to cross the bend of the elbow);
4. For patients NOT on Coumadin / warfarin, international normalized ratio (INR) ≤1.5;
5. Able and willing to give informed consent;
6. Anticipated life expectancy of at least 1 year.

Additional inclusion criteria on Day 0 (intraoperative):

7. Both vessels have been exposed and are deemed appropriate for implantation (i.e.

based on the surgeon's opinion, artery is of adequate size, has adequate pulse to support AV access flow and is safely clampable (i.e. artery has lack of significant calcification); and the vein is of adequate size, free of localized sclerosis, and is free of immediate outflow obstruction).

5.4 Exclusion Criteria

Patients will be excluded from the study for:

1. History or evidence of severe cardiac disease (New York Heart Association [NYHA] Functional Class III or IV), myocardial infarction within 6 months prior to enrollment, ventricular tachyarrhythmias requiring continuing treatment, or unstable angina;
2. Diabetes with hemoglobin A1c (HbA1c) > 10%;
3. For upper arm straight configuration, antecubital fossa crease to axillary crease distance < 18 cm;
4. History or evidence of severe peripheral arterial disease in the extremity selected for implant (i.e. arterial inflow insufficient to support hemodialysis access);
5. Known or suspected central vein stenosis or obstruction on the side of planned graft implantation;
6. In the opinion of the investigator, baseline hypotension, or history of frequent hypotensive episodes during dialysis that puts the patient at increased risk of graft thrombosis;
7. In the opinion of the investigator, uncontrolled hypertension;
8. Baseline hemoglobin <8 g/dL;
9. Baseline platelet count <100,000 or >500,000 cells/mm^3;
10. Documented history of stroke within 6 months prior to enrollment;
11. Treatment with any investigational drug or device within 30 days prior to enrollment;
12. Female patients who are pregnant, intending to become pregnant, nursing or intending to breastfeed during the study (pregnancy test may only be omitted, if patient is post-menopausal or has a documented history of hysterectomy);
13. History of cancer with active disease or treatment within the previous year, except for non-invasive basal or squamous cell carcinoma of the skin;
14. Immunodeficiency including documented history of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) or patients receiving immunosuppressive therapy for treatment of an acute inflammatory event or autoimmune flare. Chronic immunosuppressive therapy is acceptable;
15. Documented or suspected hypercoagulable state;
16. Bleeding diathesis, other than that associated with ESRD;
17. Documented history of heparin-induced thrombocytopenia (HIT);
18. Active local or systemic infection as documented from the medical history or bloodwork / blood culture data. If the infection resolves, the subject must be at least one-week post resolution of that infection before implantation;

19. Scheduled renal transplant within 6 months;
20. Any other condition which in the judgment of the investigator would preclude adequate evaluation of the safety and effectiveness of the InnAVasc AVG.

6 STATISTICS AND DATA ANALYSIS

6.1 Statistical Methodology

Summary statistics will be provided for primary and secondary study endpoints and other variables of interest as appropriate. Continuous data will be summarized via means, medians, standard deviations, ranges, and confidence intervals. Dichotomous variables will be summarized via counts, percentages, and 95% lower exact binomial confidence intervals.

Categorical variables will be summarized via counts and percentages. Graphical presentations may be provided for select study outcomes. No hypothesis testing is defined for any of the study endpoints.

The following definitions will be applied:

Table 1: *Patency, Sustained Use, and Technical Success Definitions*

Technical success	Procedure conclusion by successful implantation of the study device with a patent graft
Successful cannulation	Two-needle dialysis session through the study device
Functional patency	AV access that can be cannulated with two dialysis needles for at least 75% of dialysis sessions within a 4-week period to achieve the prescribed dialysis
Primary patency	Interval from the time of access placement until any intervention designed to maintain or reestablish patency, access thrombosis, or the time of measurement of patency
Assisted primary patency	Interval from the time of access placement until access thrombosis or the time of measurement of patency, including intervening manipulations (surgical or endovascular interventions) designed to maintain the functionality of a patent access
Secondary patency	Time from placement of the AVG to abandonment, including surgical or endovascular interventions designed to reestablish AVG patency
Sustained use	Period of time in which the study graft is used for consecutive dialysis sessions without the requirement for alternative hemodialysis vascular access to allow for renal replacement therapy

6.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is defined as secondary patency at 6 months.

- Secondary patency is defined as the time from placement of the AVG to abandonment, including surgical or endovascular interventions designed to reestablish AVG patency.[32]

6.3 Primary Safety Endpoint

The primary safety endpoint is the incidence of adverse events of special interest (AESIs) through 6 months, defined as:

1. Infection of the study device;
2. Pseudoaneurysm formation at any point along the access circuit requiring surgical/ endovascular intervention, including thrombin injection and compression (pseudoaneurysms that occur at sites of needle cannulation, but which are small enough to be observed without intervention, do not trigger this element of the AESI endpoint);
3. Bleeding from the access circuit requiring surgical/ endovascular intervention or ≥2-unit blood transfusion;
4. Hematoma from the study device requiring intervention;
5. Seroma from the study device requiring intervention
6. Thrombosis of the study device.

6.4 Success Criteria

There are no prespecified study success criteria as neither primary endpoint will undergo hypothesis testing. However, device safety and efficacy will be compared to the relevant literature for early cannulation grafts considering patency rates at 6, 12, 18, and 24 months as well as complication rates over 2 years.

6.5 Secondary Endpoints

The following secondary endpoints will be collected and assessed via summary statistics:

1. Functional patency at 3, 6, 12, 18 and 24 months;
2. Time to successful cannulation, defined as the time from the index procedure to the first 2-needle dialysis session through the study device;
3. Proportion achieving sustained use of 3 months, 6, months, 12 months , 18 months and 24 months. Sustained use is a period of time in which the study graft is used for consecutive dialysis sessions without the requirement for alternative hemodialysis vascular access to allow for renal replacement therapy. A sustained use period can be achieved at any time throughout the study period of 24 months.

6.6 Exploratory Endpoints

Unless otherwise specified, all exploratory endpoints will be assessed at 3, 6, 12, 18 and 24 months.

The following exploratory endpoints will be collected and assessed via summary statistics:

1. Primary patency rate;
2. Assisted primary patency rate;
3. Days of central venous catheter *in situ*;
4. Incidence of individual adverse events;
5. Change from baseline patient reported outcomes measures (PROM) / patient reported experience measures (PREM) survey;
6. Health Economics based on collected study data, e.g.
    a. Overall cost to create and maintain AV access
    b. Catheter related costs
    c. Cost of AV access related complications.

6.7 Trial Population

The Intention-to-Treat Population (ITT) includes all subjects in whom the host vessels have been deemed appropriate by the investigator for placement of an AVG and the investigator has made the decision to proceed with implantation of the investigational device. Subjects with technical failures will not be excluded from the ITT.

6.8 Missing Data

Every effort will be made to minimize the amount of missing data. The amount of and reasons for missing endpoint data will be provided in the final report. The primary analyses in the clinical study report will be based on available data; however, a number of sensitivity analyses will be performed including best- and worst- case analyses to help assess the potential impact of missing data.

6.9 Primary Safety Endpoint Sample Size

A literature review was conducted to estimate the incidence of AESIs associated with other ePTFE grafts through 6-months. The results provided in Table 1 show that the adverse event (AE) profile associated with ePTFE grafts in general is well-understood and that individual AEs of special interest would be expected to occur at incidence levels ranging from 5%-12%.

A sample size of 60 treated subjects provides a high likelihood identifying unique AEs associated with the use of the InnAVasc graft, thereby properly characterizing its risk profile. In particular, 60 treated subjects study will mean a greater than 95% chance to detect an AE that would occur at an underlying rate of 5% and a greater than 99% chance to detect an AE that would occur at an underlying rate of 8%.

6.9.1 Table 2: Incidence of Device Related Adverse Events in ePTFE Grafts

Adverse Event	6-month incidence estimate for ePTFE grafts	Literature Support and Estimate Calculation
Infection	5% - 20%	• 4% - 20% per year for prosthetic AV access with 7 sources cited, survey from Centers for Disease Control [CDC] - average of 3.2% of patients per month at dialysis centers[27] • 11% @ 1 year (138 pts)[33]
Pseudo-aneurysm	5 - 10%	• range from 2-10% in ePTFE grafts with 3 sources cited, 0.049 to 0.1 per patient-year from two randomized trials[27] **Note**: (0.1 events per patient year [EPPY] * 30 patient years = 3 events, 3 events / 60 = 5%)
Hematomas	4-10%	• Incidence ranges from 0.073 – 0.2 per patient year with 2 sources cited[27] • 4% @ 1 year (138 pts)[33] **Note**: 0.2 EPPY * 30 patient years = 6 events, 6 events / 60 =10%
Bleeding	12%	• 0.24 EPPY[34] **Note**: 0.24 EPPY * 30 patient years = 7.2 events, 7.2 events / 60 = 12%

6.10 Primary Effectiveness Endpoint Sample Size

The primary endpoint of secondary patency at 6 months post-procedure was assessed from a literature review of secondary patency rates, where a meta-analysis on the basis of 34 relevant studies found the cumulative patency rate to be 76% at 6 months for arteriovenous grafts.[35]

Secondary patency in this study is defined as the time from placement of the AVG to abandonment, including surgical or endovascular interventions designed to reestablish AVG patency.[32]

Utilizing a simple asymptotic one-sided calculation in Power Analysis and Sample Size

(PASS) 2013 software to provide a lower, one-sided 95% confidence bound shows that a primary effectiveness success rate of 76% would have a lower confidence bound of 65.29%, or a distance of just over 10% from the estimate to the bound limit. In the event the study realized a 5% subject loss, there would be minimal impact to the confidence bound calculation as a sample size of 57 subjects with a 76% success rate would elicit a lower bound of 64.9%. Sample size calculations were performed in PASS 2013 utilizing an exact Clopper-Pearson calculation method and a one-sided, lower 95% confidence bound.

Therefore, the proposed sample size of 60 subjects will provide a highly confident understanding of where the true secondary patency rate at six months associated with use of the InnAVasc graft lies.

6.11 Changes to Planned Analyses

Any changes to the planned analyses will be documented in the study report.

6.12 Assessment of Data Poolability

Poolability of data across clinical study sites is justified on a clinical basis (i.e. all study sites use the same protocol, the sponsor monitors the site for protocol compliance, and the data gathering instruments are identical).

Poolability will also be assessed visually via presentation of primary and secondary study endpoints, as well as key baseline variables by study center. No statistical method is proposed to assess poolability due to the lack of hypothesis testing associated with the primary study endpoints. Differences between study sites will be investigated and elucidated in the study report.

6.13 Enrollment

Enrollment is competitive, but in order to reduce instance of a significant center effect, there will be an enrollment cap of 32% (19 subjects) per center.

7 ASSESSMENTS AND FOLLOW-UP SCHEDULE

Subjects will undergo the assessments outlined below.

7.1 Screening/Baseline Visit (Day -45 to Day 0)

An initial evaluation will be used to determine if a subject may be considered for treatment. This evaluation includes an assessment of diagnostic testing that would have been done as part of a subject's routine care.

The data captured for the Screening Visit may be gathered over the course of more than one office visit; however, the data must have been obtained within 45 days of the scheduled procedure date.

The following procedures will be performed at the Screening Visit prior to the procedure. All data must be recorded in the subject's case report form (CRF):

- Informed consent
  - The subject's informed consent must be obtained prior to commencement of any study-related procedures/activities, using the site's Institutional Review Board (IRB) approved consent form. Standard of care procedures such as vitals or laboratory evaluations conducted prior to Screening may be used to fulfill screening requirements rather than repeating the test providing they are within the Screening period time window and all required data are available. The informed consent will cover each of the following:
    - Agreement to participate in the study for the full 2 years;
    - Agreement to wear the study ID band and/or carry the cannulation template which provides the QR code link to the cannulation instruction animation video.
    - Willingness to have study-specific medical information collected if the subject desires to stop coming for study visits. It should be noted that consent for this information collected is not a requirement for participating in the study;
    - Willingness to have part of the InnAVasc AVG collected for histology (if explanted for clinical reasons). It should be noted that consent for collection of histology is not a requirement for participation in the study.

- Demographic information

- Medical history including risk factors

- Laboratory tests (within 45 days of index procedure)

- Prior and concomitant medications

- Physical examination
- Vessel mapping (if not done within 8 weeks; to ensure suitability of the implantation site and to exclude central vein stenosis on the side of graft implantation (if there is a suspicion for central venous obstruction))
- Review inclusion/exclusion criteria
- Adverse events (occurring from a research only procedure)
- Patient-reported outcomes questionnaire
- Clinical laboratory tests
  - Clinical laboratory tests will be performed at this visit to establish baseline levels. It is recognized that specific panels may vary between institutions. Laboratory data will not be specially analyzed but will be used only to support AE evaluations. The following must be collected:
    - Complete blood count (CBC) [platelets and hemoglobin]
    - HbA1c
    - INR
    - Pregnancy test (unless no childbearing potential)

7.2 Treatment (Day 0)

Implantation of the InnAVasc AVG is considered the treatment phase of the study. Refer to **Section 2.8** above and/or to the **Instructions for Use (IFU)** for techniques and methods for device deployment.

Subjects who require interventions to salvage the AVG, explantation of the AVG or the insertion of a central venous catheter due to treatment failure with the device will be followed at each of the follow-up visits specified in Table 2.

The following data are to be recorded on the subject's CRF.

- Concomitant medication
- Confirmation of inclusion/exclusion criteria
- Device placement location and configuration (looped or straight)

- Required adjunctive therapy and additional procedures prior, post and/or during procedure
- Confirmation of patency while the subject is in the operating room/ recovery room using physical exam (palpation or auscultation), or Doppler exam;
- InnAVasc Graft first use;
- Documentation of InnAVasc Graft use and patency beyond D0;
- AE observation, evaluation, and treatment.

Prior to discharge the subject will be instructed to contact the study staff promptly if he/she develops new or worsening pain, redness, local swelling or bruising around the surgical site or the graft or any generalized swelling of the operative arm. If such symptoms occur and the investigator considers that they might be clinically significant an additional unscheduled visit should be scheduled. (As a minimum, AEs and concomitant medication should be recorded at an unscheduled visit.) Each subject will be provided with contact information for use in such circumstances. These instructions will be repeated at every study visit. The dialysis unit treating the subject will be notified that the subject is participating in the study and will be asked to contact the study staff urgently if they have any concerns about the graft. The subjects will be provided with the study ID band and cannulation template which are both equipped with the QR code link the "how to" cannulation animation video.

7.3 Follow-Up Assessment

Formal, in person follow-up evaluation will be scheduled for 14 days (+/- 5 days) 45 days (+/- 7 days), 6 months (+/- 14 days), 12 months (+/- 30 days), and 24 months (+/- 30 days) post-procedure.

During months 1, 3, 4, 5, 9 and 18 (+/- 7 days), telephone contact will be made with the dialysis unit to check on the status of the subject. At ALL study assessment time points, the dialysis records will be obtained to conduct an accurate assessment of the interval history with the recorded study graft related AEs, cannulation related events, known interventions, and graft function/patency information. An additional step to ensure that all the AEs have been captured with these time intervals, will consist of direct contact of the subject by the study coordinator to capture any safety or intervention information that might have been missed by the dialysis unit. The following assessments and procedures will be performed at the scheduled follow-up visits/assessments:

7.3.1 Day 14 (± 5 days)

- Concomitant medication
- Adverse events
- InnAVasc graft use for HD
- Documentation of InnAVasc Graft patency
- Examination of access site
- Documentation of InnAVasc graft interventions
- Directed PE to evaluate AEs
- Patient reported outcomes questionnaire

7.3.2 Month 1 (M1) – Telephone (± 7 days)

- Adverse events
- Dialysis access use/patency
- Documentation of graft interventions

7.3.3 Day 45 (D45) - (± 7 days)

- Documentation of InnAVasc Graft patency
- Concomitant medication
- Adverse events
- InnAVasc graft use for HD
- Examination of access site
- Documentation of InnAVasc graft interventions
- Patient-reported outcomes questionnaire

7.3.4 Month 3 (M3) - Telephone (± 7 days)

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions

7.3.5 Month 4 (M4) - Telephone (± 7 days)

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions

7.3.6 Month 5 (M5) - Telephone (± 7 days)

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions

7.3.7 Month 6 (M6) (± 14 days)

- Concomitant medication
- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Examination of access site
- Documentation of InnAVasc graft interventions
- Duplex ultrasound examination (patency, flow, and monitoring of entire graft length for aneurysm development)
- Patient-reported outcomes questionnaire

7.3.8 Month 9 (M9) - Telephone (± 7 days)

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions

7.3.9 Month 12 (M12) (± 30 days)

- Concomitant medication

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Examination of access site
- Documentation of InnAVasc graft interventions
- Patient-reported outcomes questionnaire

7.3.10 Month 18 (M18) - Telephone (± 7 days)

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions

7.3.11 Month 24 (M24) / Early Termination (ET) (± 30 days)

- Concomitant medication
- Physical examination
- Adverse events
- Dialysis access use
- Examination of access site
- Documentation of InnAVasc graft interventions
- Patient-reported outcomes questionnaire

7.4 Assessment of Patency

Patency and dialysis access use will be assessed at all visits (except Screening). For in person visits, patency will be assessed by investigator preference, by one of four methods: Palpation, auscultation, Doppler, or ultrasound.

For telephone visits, patency will be assessed by dialysis unit treatment sheets. The InnAVasc graft will be considered patent if any of the following is documented:

- Palpation of thrill;
- Auscultation of bruit;
- Successful dialysis with one or two needles via the InnAVasc graft

7.5 Dialysis Procedures

Hemodialysis via the InnAVasc Graft is allowed as early as the same day as implant. **For purposes of this clinical investigation, the expectation is that the first use of the InnAVasc AVG for two needle HD will occur on the same day as implant, or the next day, but not beyond 7 days post implant as long as medically appropriate.** Dialysis should be initiated using small needles (17G or 16G). This needle size should be used for at least the first 2 weeks of dialysis using the InnAVasc AVG. After 2 weeks the needle size may be increased and standard needles (no greater than 14G) may be used. Needle placement sites should be rotated using a rope - ladder technique to allow for healing of the skin, and to reduce graft material degradation secondary to area cannulation, and thus minimize the possibility of aneurysm formation or complication. A cannulation template will be provided for each subject participating in the study to ensure that proper needle site rotation is heeded during the study. The provided cannulation template and study ID bands are both equipped with the QR code link the "how to" cannulation animation video, which is in addition to education provided to the dialysis units and technicians from the dialysis organization education team and additional training direct from the Sponsor. Since the InnAVasc graft is an immediate use dialysis access graft, we will require proper skin preparations and sterile technique (including sterile glove use) prior to each cannulation occurring within the first 30 days post implant. The InnAVasc graft features self-sealing properties, but gentle pressure should still be applied to needle puncture sites post needle withdrawal for at least 60 seconds (or until bleeding stops) to prevent skin capillary bleeding. There is no need for application of a pressure dressing to needle puncture sites.

7.6 Patient Reported Outcomes Survey

All subjects will be asked to respond to a short questionnaire with a focus on patient reported outcome measures (PROMs) and patient reported experience measures (PREMs) specific to hemodialysis access. The survey features approximately 12 questions (approximately 5-10 minutes to complete) that focus on technical aspects of vascular access, emotional concerns, pain and anxiety around vascular access, and logistical issues. The survey is administered in the study site clinic, during specified study visits at: Screening, D14, D45, M6, M12, and M24.

7.7 Secondary Interventions

Subsequent to treatment, conditions warranting additional treatment (e.g., thrombosis, stenosis, etc.) may present. Any intervention taken to treat a condition involving the InnAVasc AVG shall be documented on the Additional Treatment CRF. Additional InnAVasc AVG devices may be provided for conditions involving the initially-treated lesion. Since such procedures would be secondary interventions, repeating the determination of eligibility and consenting are not required unless mandated by institutional policies.

Additional InnAVasc AVG devices may not be used for other conditions without prior written approval from the Sponsor. Such procedures must be presented in advance to the competent authorities and Institutional Review Board (IRB) unless deemed emergent. In either case, the use of the InnAVasc AVG device for other lesions/conditions shall be treated as a protocol deviation.

7.8 Early Termination Visit

The subject may withdraw from the study at any time at their own or their physician's discretion. If withdrawal occurs before the M24 visit, the subject will be asked to complete an early termination visit at which all assessments normally performed at M24 will be completed. The reasons for early termination should be recorded in the CRF.

7.9 Unscheduled Post Treatment Follow-up Visits

If a subject returns to the institution between scheduled follow-up visits for matters related to the study procedure, the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the Investigator. CRF pages are provided for unscheduled visits and contain the same information as all the follow-up visits, in addition to the reason for the visit. Dialysis units are instructed to refer study subjects back to the investigator immediately if any adverse event, cannulation related issues, or safety concerns are identified in or around dialysis treatments.

7.10 Withdrawals and Loss to Follow-up

Participation is completely voluntary, and each subject is free to withdraw from the study at any time. An investigator also has the right to withdraw the subject from the study in the event of reasons concerning the health or well-being of the subject, or in the case of lack of cooperation. Should a subject decide to withdraw for any reason, or should the investigator decide to withdraw the subject, all efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal must be made and an explanation given of why the subject is withdrawing or being withdrawn from the study.

The reason for and date of withdrawal must be recorded on the subject's End of Study CRF. If the reason for the withdrawal is a device-related or procedure-related AE, the event must be reported to the Sponsor and recorded in the CRF.
If the index surgical implant procedure is aborted, the subject does not need to complete the follow-up assessments. In that circumstance, an Early Termination (ET) visit should be performed.

If a subject dies during the course of the study, the Sponsor will request an autopsy provided the subject authorized an autopsy in the event of death during the course of the study. Autopsy observations should include documentation of condition of body organs and determination of device and/or procedure relationship to death.

All efforts will be made to retain subjects in order to collect data at all the follow-up visits (14 days through 24 months). Due diligence in reaching the subject must be made by:

- Two documented telephone contact attempts, emails, or regular postal mail letters; and
- Certified letter

After the above attempts were made, if no response is obtained, the final evaluation of a given subject will be the last visit at which study-related procedures were performed on that subject. The End of Study CRF page will need to be completed and communication attempts will need to be documented.

7.11 Study Duration

The total study duration (first subject enrolled to the last subject's final study visit) is expected to be approximately 34 months. The total duration for each subject's participation is expected to be 25.5 months.

7.12 Histological Examination of Resected InnAVasc AVG Material

If all or part of the InnAVasc AVG is resected it should, wherever possible, be retained for future histological examination. Instructions for preservation, storage and shipping of this material will be provided separately in a procedures manual. If a subject dies with an InnAVasc AVG in situ and it is feasible to obtain a fresh post mortem sample of the graft this should be attempted in accordance with local regulations.

8 STUDY MANAGEMENT CONSIDERATIONS

8.1 Protocol Modifications

No changes from the final approved (signed) protocol will be initiated without the IRB's prior written approval or favorable opinion of a written amendment, except when necessary to eliminate immediate hazards to the subjects or when the change involves only logistics or administration. The Principal Investigator will acknowledge the amendment by signing the Protocol Agreement.

8.2 Protocol Deviations

A protocol deviation is the non-adherence to or divergence from the protocol-specific study procedures. For example, violations of the inclusion and exclusion criteria, deviations from the schedule of required follow-up assessments, improper or lack of consent, and lack of IRB approval, would all be considered protocol deviations. A protocol deviation undertaken to protect the life or physical well-being of the subject in an emergency is a special circumstance that must be reported to the Sponsor and the reviewing IRB within 5 working days. The Sponsor must report the deviation to the FDA within 5 working days after the Sponsor learns of the deviation. No other type of prospective protocol deviation is permitted without prior approval. A record of all protocol deviations will be maintained and reviewed throughout the conduct of the study. The Sponsor will address deviations and take appropriate corresponding action. Continued non-compliance with the study protocol may lead to termination of the Investigator's participation in the study.

8.3 Information to Study Personnel

The Investigator is responsible for giving information about the study to all staff members involved in the study or in any element of subject management, both before starting the study procedures and during the course of the study (e.g., when new staff become involved). The Investigator must ensure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities.

The sites will be trained on the protocol and device by the sponsor or designee.

9 ASSESSMENTS OF SAFETY

9.1 Definitions

9.1.1 Adverse Event

An adverse event (AE) is an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

- This definition includes events related to the procedures involved.

Adverse events are rated in several ways:

- Severity (mild, moderate, severe)
  - ***Mild*****:** No limitation of usual activities, no therapy or only symptomatic therapy required to treat the injury or illness.
  - ***Moderate*****:** Some limitation of usual activities or specific therapy is required.
  - ***Severe*****:** Inability to carry out usual activities, hospitalization, emergency treatment, life threatening events, or death.
- Anticipated (anticipated, not anticipated)
- Device and procedure relationships (unrelated, possibly related, or definitely related)
  - ***Unrelated:*** The clinical event is completely independent of study procedure/study device and/or evidence exists that the event is definitely related to another etiology.
  - ***Possibly related:*** The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to "possibly" suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.
  - ***Definitely related:*** The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.

9.1.2 Serious Adverse Event

A Serious Adverse Event (SAE**)** is an adverse event that

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or
2) a permanent impairment of a body structure or a body function, or
3) in-patient or prolonged hospitalization, or
4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan (i.e., protocol), without serious deterioration in health, is not considered a serious adverse event.

9.1.3 Adverse Event of Special Interest

An adverse event of special interest (AESI) is a subcategory of adverse events that include any of the primary safety endpoints.

9.1.4 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

9.1.5 Adverse Device Effect

An adverse device effect (ADE) is an AE related to the use of an investigational medical device.

- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

9.1.6 Serious Adverse Device Effect

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious AE.

9.1.7 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE**)** is defined as serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Section 14.1 includes a list of possible adverse events associated with AVG implantation and use, including those events considered AESIs.

9.2 Reporting of Adverse Events and Device Deficiencies

All adverse events and device deficiencies must be via the Adverse Event Case Report Form. The report should include, whenever possible, severity, duration, outcome, and the Investigator's medical judgment as to the relationship of the adverse event to the study device, procedure, or underlying disease (i.e., not related, possibly related, or definitely

related).

All SAEs and device deficiencies that could have led to a SADE must be reported to the Sponsor or its Contract Research Organization (CRO) within 1 business day of the Investigator's knowledge of the event using the SAE report form. IRB notification of the AE may also be required, depending on the conditions of approval or requirements of the respective committee.

Emergency contact details for reporting SAEs and device deficiencies that could lead to SADEs are specified below:

Study initiation to 6 months:

SCOPE International Pharmacovigilance

E-Mail: safety@scope-international.com

Fax: +370 52 327 903

Tel: +370 52 360 349

Beyond 6 months (for each patient), safety reporting transitions to:

TAB Clinical Pharmacovigilance

E-Mail: dbuckley@tabclinical.com

Fax: 919 882 1451

Tel: 919 694 5454

Following notification by the Investigator, the Sponsor will immediately conduct an evaluation of the event(s) and SCOPE Pharmacovigilance or the Sponsor will report USADEs and device deficiencies that could have led to a SADE to all participating IRBs, Investigators, and FDA on expedited basis, as required by the FDA within 10 working days after the Sponsor first receives notice of the adverse effect.

Certain reportable events may require adjudication; therefore, supporting documentation must be sent to the Sponsor/CRO, as requested.

9.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be responsible to assure the study is being conducted ethically and to adjudicate all possibly and definitely device and/or procedure-related serious adverse events. The DSMB membership is represented from the key medical disciplines involved with the care of ESRD patients and the creation and management AV access, and includes a biostatistician. None of the members is directly

involved with the clinical trial and all possess experience with clinical trial participation or management in the ESRD or AV access space. The Sponsor has contracted a third party to organize, facilitate, and document meetings for the DSMB for this trial. The DSMB will meet regularly and as necessary, guided by a DSMB charter.

Since this study has been designed to sufficiently characterize effectiveness and safety outcomes, the study does not contain hypothesis testing to statistically assess study success. As such, the DSMB will make recommendations on protocol modifications and continuation of the study based on what the relevant literature provides as expected ranges for success in both primary effectiveness and safety. This will provide a mechanism to visually assess the comparability of the study results relative to prior, relevant research. These metrics are explained and defined within the DSMB charter.

10 DEVICE ACCOUNTABILITY

10.1 Accountability and Procedures

a.) Each device shipment must be documented on the Device Accountability Log and include the receipt, dispensing, and return of investigational devices.

b.) When a shipment is received, the Investigator (or designee) must record on the Device Accountability Log the date received and the Catalog and Lot Number of each device. It is recommended that the Packing List also be signed and dated.

c.) Investigational devices must be kept in a secure, limited access storage area under recommended storage conditions (room temperature).

d.) During the course of the study, the following information must also be noted on the Device Accountability Log:

- Identification number of the subject for whom the device was intended
- Procedure date

e.) The Device Accountability Log must be readily available for inspection by representatives from the Sponsor, the IRB, and/or other relevant regulatory authorities at any time.

f.) The Device Accountability Log and device storage locations will be reviewed during monitoring visits.

g.) All unused investigational devices must be returned to InnAVasc Medical, Inc. once it is determined they will not be used. Upon completion of the study, all unused investigational devices must be returned to InnAVasc Medical, Inc., if any remain at the site. The monitor is to verify return.

11 STUDY ADMINISTRATION

11.1 Site Initiation

A Site Initiation Visit (SIV) will be conducted by the Sponsor or other appropriate designee, for example, its contract research organization (CRO), to ensure that all study supplies are present, to ensure proper training of the Investigator and study staff members in study-specific procedures, to ensure regulatory requirements are fulfilled prior to enrollment of the first study subject at a site, and to verify the site facilities and equipment are appropriate for conduct of the study.

11.2 Training and Oversight of Dialysis Units

Although neither the dialysis organizations nor the individual dialysis units are study sites, the dialysis units and staff will play an integral role in documenting safety and effectiveness information required for the study or reporting safety concerns to the investigator sites. The information required for the clinical study is part of the standard medical record and will be requested from the dialysis units by the investigator at each study visit/communication date listed in the Schedule of Assessments table (Table 4). This will ensure that all pertinent safety and effectiveness information is collected throughout the duration of the clinical trial.

In advance of first access, the Sponsor will ensure that the dialysis staff accessing the graft is trained via a platform agreeable to the dialysis center. Training documentation will be collected by the sponsor and will be filed in the trial master file (TMF). The sponsor will be available for questions from the dialysis centers during usual dialysis center business hours. In addition, the provided cannulation template and study ID bands are both equipped with the QR code link the “how to” cannulation animation video. This will help to serve as an adjunct to initial training, but will also serve as cannulation training in the event that a subject is admitted to another dialysis unit or hospital without the primary dialysis unit, the subject’s PI, or study Sponsor being notified.

Specific attention should be paid to needle cannulation related AEs in and around the InnAVasc graft cannulation sites. Information essential to document should include (but not limited to) what is provided in the list below:

a. Missed graft puncture attempt
b. Hematoma formation (during HD, or post needle withdraw)
c. Identification of Pseudoaneurysm development
d. Bleeding from graft (> 10 min)
e. Infection present at access site
f. Ulcers or eschar development
g. Skin erosion

h. Suspected backwall puncture

i. Elevated pressures in graft circuit

j. Needle displacement during dialysis.

k. Wounds or complications at the access site

11.3 Study Monitoring

Interim monitoring visits will be conducted by InnAVasc Medical, Inc., personnel or other appropriate designees (e.g., a CRO) to ensure compliance with standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines.

The study monitor will contact and visit the Investigator at regular intervals throughout the study (refer to Monitoring Plan for details). The monitor will be allowed to check and verify the various records (CRFs and other pertinent source data records) relating to the study to verify adherence to the protocol and to ensure the completeness, consistency, and accuracy of the data being recorded.

As part of the supervision of the study progress, other Sponsor personnel may accompany the study monitor on visits to the study center. The Investigator and assisting staff must agree to cooperate with the study monitor to resolve any problems, errors, or possible misunderstandings concerning the findings detected in the course of these monitoring visits.

11.4 Study Termination

InnAVasc Medical, Inc. and applicable regulatory authorities have the right to terminate the entire study or a study site at any time. Situations that could warrant study termination include, but are not limited to:

a) Increased incidence of adverse experiences and/or the severity of such, suggestive of a potential, device-related health hazard

b) Insufficient subject enrollment

c) Recurrent protocol non-compliance, violations or deviations

d) Inaccurate, incomplete, and/or untimely data recording (>2 business days) on a recurrent basis

e) Lack of cooperation with monitoring visits (e.g., failure to adequately prepare for visits, address action items from one visit to the next, or provide access to medical records)

11.5 Data Handling and Recordkeeping

11.5.1 Completing, Signing and Archiving Case Report Forms

The investigator must keep a separate subject identification list showing enrollment

numbers, names, and dates of birth to allow unambiguous identification of each subject included in the study. It is recommended a note be made in the medical record that the subject is participating in a clinical research study.

The required data will be recorded on CRFs. Clinical study data will be collected using electronic case report forms (eCRFs). A web-based electronic data capture (EDC) database will be used to record and manage study data. eCRF completion guidelines, the instructions for electronic data-entry, will be developed in conjunction with the sponsor, the CRO, and/or the EDC vendor. The CRFs will be completed electronically or legibly in black or blue ink, with reasons documented for missing data. All eCRFs must be kept in good order and updated so they always reflect the latest observations on the subjects participating in the study.

The Investigator will sign the appropriate pages of the CRF and source documentation. eCRF corrections will be made electronically and signed electronically by the Investigator. An embedded audit trail will capture the date, time and user making updates and changes to the electronic data.

Because it is important to have proper data collection in a timely manner, within 2 business days, the Investigator/Study Coordinator shall complete the eCRFs and provide them to the monitor upon request. When the monitor requests additional data or clarification of data for the eCRF, the request must be answered satisfactorily before the next monitoring visit.

11.5.2 Data Management and Archiving

The Sponsor will be responsible for the processing and quality control of the data. Source data for safety will be retained for at least 2 years after the termination/completion of the study or after the approval/withdrawal of the marketing application, whichever occurs later. All other source data, eCRFs, copies of protocols and protocol amendments, device accountability forms, correspondence, subject identification lists, informed consent forms, and other essential documents must be retained for a period of at least 2 years after the last approval of the marketing application and until there are no pending or contemplated marketing applications, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device.
InnAVasc Medical, Inc. will inform the Investigator/institution when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to the Sponsor.

11.5.3 Direct Access to Source Data/Documentation

The Sponsor, auditors, and health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records, (i.e., source documents) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's findings or progress notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject. All study-related documents must be kept until notification by InnAVasc Medical, Inc.

12 ETHICS

12.1 Informed Consent

Written informed consent must be obtained for each subject before any study-specific procedures or assessments are done and, specifically, prior to the subject being treated with the InnAVasc AVG. Written informed consent will be obtained after the aims, methods, anticipated benefits, and potential hazards are explained.

The subject's willingness to participate in the study will be documented in writing in a study-specific informed consent form, which will be signed and dated by the subject. The investigator will keep the original consent form and a copy will be given to the subject. It will be explained to the subjects that this is a voluntary study and they are free to withdraw from the study at any time without prejudice to future treatment.

12.2 Institutional Review Board

This study must be approved by an appropriate IRB respectively at each investigational site. The Investigator will ensure that IRB approval is obtained prior to starting the study, as defined by regulations (21 CFR §56.103 and 21 CFR §812.110(a)).

The Sponsor must receive a copy of the IRB approval letter (or equivalent documentation) for the study protocol and informed consent form before the study can be started at that site or devices shipped to that Investigator.

The IRB and Sponsor must approve any significant changes to the protocol as well as a change of Principal Investigator. Documentation of the IRB approval must be provided to the Sponsor. Records of all study review and approval documents must be maintained by the Investigator in the Regulatory Binder and are subject to inspection by the Sponsor or regulatory authority during or after completion of the study.
Unexpected Serious Adverse Events, unanticipated problems adding risk to subjects, and deaths must also be reported to the IRB and Sponsor (reference Section 10.2 for reporting instructions).

The Investigator must notify the IRB, as per their reporting guidelines, and the Sponsor when he or she deviates from the protocol. The Sponsor must be notified of all relevant action taken by the IRB and must receive a copy of all study-related correspondence between the Investigator and the IRB.

The IRB must receive notification of the completion of the study and final report within 3 months of study completion or termination. The Investigator must maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

12.3 Confidentiality Regarding Study Subjects

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an individual identification (ID) code (i.e., institutional ID and subject identification number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may conduct source-document verification on behalf of the Sponsor, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

12.4 Participating Institutions and Investigators

Study sites and Investigators will be selected based on a variety of factors including, but not limited to, experience with the surgical implantation of AV access sites, access to required facilities and equipment, sufficient and adequately trained personnel including in human clinical research, and availability of potential subjects. The criteria used for determination will be documented. No other centers/institutions are intended to participate in this study without permission from the relevant regulatory authority.

12.5 Agreements

All Principal Investigators and their Sub-Investigators or Co-Investigators must sign an Investigator Agreement. InnAVasc Medical Inc., (or the authorized CRO) must receive a copy of the signed Investigator Agreements before the study may be started at that institution or devices shipped. Any Investigators joining the study after the site has been initiated may not receive devices or participate until an agreement is signed and received by the Sponsor.

12.6 Responsibilities

Investigator responsibilities include, but are not limited to, the following:

a.) Conducting the study in accordance with this investigational plan, signed agreement, and applicable regulations protecting the rights and safety of study subjects

b.) Informing all subjects that the device being utilized is for investigational purposes only, and ensuring that the requirements relating to obtaining informed consent and IRB approval are met

c.) Ensuring that informed consent is obtained for each study subject in accordance with applicable regulations (e.g., ISO 14155-2011, ICH GCP, 21 CFR Part 50)

d.) Ensuring that IRB approval is secured prior to starting the study and ensuring continuing review and approval as required throughout the investigation

e.) Ensuring all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations, are adequately qualified and trained, and meet their commitments

f.) Maintaining adequate and accurate records and ensuring those records are available for inspection at any time

g.) Ensuring that conducting the study does not give rise to conflict of interest (financial disclosure is required)

h.) Controlling of all investigational devices under investigation.

13 DATA SECURITY AND SCIENTIFIC INTEGRITY

13.1 Access to Data

The Sponsor, auditors, and health authority inspectors (or their agents) will be given access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

The Investigator must maintain, at all times, the primary records (source documentations) of each subject's data. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, device inventory, device label records, and CRFs that are used as the source.

The Investigator will maintain a confidential subject identification list that allows the unambiguous identification of each subject.

13.2 Security and Confidentiality

The Investigator must ensure that the privacy of all subjects, including their personal identity and all personal medical information, will be maintained at all times. In CRFs and other documents or image material submitted to the Sponsor, subjects will not be identified by their names, but by an identification code (i.e., subject number).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRFs. The monitor may perform source data verification on behalf of the Sponsor or regulatory authorities. Personal medical information will always be treated as confidential.

13.3 Electronic Data

Electronic data will only be accessible to authorized personnel through the use of a unique user identifier and password. Passwords are set to expire periodically. Access to electronic study data will be provided to research personnel upon completion of training. Read and write access will be provided to investigational sites but only for information and subject data at their own site. The CRO will have read-only access and can post queries for potential data-related discrepancies.

14 RISK ANALYSIS

14.1 Risks to the Subjects

Treatment with the InnAVasc AVG is a procedure that poses significant risks to the subject, although these risks are not expected to be greater than with the current standard of care AVGs presently available. A summary of some of the known risks are identified in **Table 3**; however, there may be risks that are not known or are unforeseen at this time. The risks include those related to the device and to the procedure, including those related to concomitant medications used periprocedurally and during follow-up.

***Table 3**: Known Risks of Arteriovenous Graft Implantation*

Event Category	Event
Bleeding	Early, postoperative
	Prolonged bleeding from needle puncture site
Infection	Early infection, during procedure
	Late infection, due to cannulation
Noninfectious fluid collections	Hematoma
	Seroma
	Lymphocele
Anastomotic complications	Hemorrhage
	Pseudoaneurysm
	Stenosis with intimal hyperplasia
Mid-AV access/runoff vein complications	Dilation/aneurysm
	Pseudoaneurysm at needle stick site
	Mid-AV access stenosis
AV access malfunction	Insufficient inflow
	Insufficient runoff
	Inability to puncture
Ischemia	Steal syndrome
Cardiac	Myocardial infarction

Table 3. Known Risks of Arteriovenous Graft Implantation

Event Category	Event
	Congestive heart failure
	Arrhythmia
	Valve disorders; stenosis and insufficiency
	Hypertension
	Hypotension
Wound	Wound infection
	Wound pain
	Wound dehiscence
	Serous wound drainage
	Lymphorrhea
	Hematoma
	Ecchymosis
Venous	Deep venous thrombosis
	Pulmonary embolism
	Paradoxical embolization
	Venous hypertension
Local	Arm edema
	Arm pain
	Back pain
Cerebrovascular	Transient ischemic attack
	Stroke
	Intracranial hemorrhage
Genitourinary	Urinary retention
	Urinary tract infection
	Renal stones
	Renal insufficiency, failure
	Hematuria

Table 3. Known Risks of Arteriovenous Graft Implantation

Event Category	Event
	Impotence and other disorders of sexual function
Pulmonary	Exacerbation of chronic lung disease
	Pneumonia
	Pulmonary embolism
	Respiratory failure
	Bronchitis
	Bronchospasm
Gastrointestinal	Peptic ulcer disease
	Reflux esophagitis
	Nausea and vomiting
	Diarrhea
	Constipation
	Hepatitis
	Hepatic insufficiency
	Cholelithiasis / cholecystitis
Metabolic/systemic disorders	Electrolyte imbalances
	Hyperglycemia
	Hypoglycemia
	Fluid overload
	Dehydration
	Thrombocytopenia
	Leukopenia
	Anemia with or without need for transfusion
Miscellaneous	Sepsis
	Skin erosion

Table 3. Known Risks of Arteriovenous Graft Implantation

Event Category	Event
	Compartment syndromes
	Psychiatric disorders including depression
	Mental status changes
	Insomnia
	Allergic reactions to device components
	Allergic reactions to concomitant medications

There are other health risks and discomforts associated with the testing that the subjects will undergo before and after their procedure, including, but not limited to, bruising during blood collection, pain and bruising at the access site and radiation exposure during imaging procedures.

14.2 Risk Mitigation

The Sponsor designed the InnAVasc AVG and the clinical investigational protocol to minimize risks to the study participants. Study eligibility criteria were formulated to limit use of the study device to subjects that fit the device specifications. Evaluation of safety data by an independent DSMB will provide an ongoing assessment of safety- related events, both individually and in aggregate.

14.3 Benefit to Subjects

It is hoped that the InnAVasc AVG will provide an additional improved treatment option for patients with ESRD requiring hemodialysis. The InnAVasc AVG has several advantages over many of the AVGs that are currently available. The InnAVasc device may reduce the number of complications associated with the implantation and use of AVGs. For example, the InnAVasc AVG can be cannulated immediately, reducing the need for the insertion of a temporary CVC and thereby eliminating exposure of the patient to CVC associated infections and complications. In addition, the design of the InnAVasc AVG aims to reduce graft injury due to improper cannulation and allows for easier cannulation. Lastly, this device is designed to reduce graft compression and the resulting interruptions in blood flow.

14.4 Study Justification

This study is justified considering previous work showing positive outcomes obtained through use of the InnAVasc AVG. This study will attempt to build on past results and, potentially, identify additional benefits of AV access grafts in patients with ESRD.

15 PUBLICATION POLICY AND PUBLIC DISCLOSURE

The information generated by this trial is the property of InnAVasc Medical, Inc. InnAVasc Medical, Inc. will appropriately publish the results of this clinical trial in accordance with all applicable regulations.

This study will be listed in the www.clinicaltrials.gov database, and results will be posted following the end of the study.

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17 Table 4: Schedule of Assessments

Assessment	Screening/ Baseline (Day -45 to Day 0)	Treatment (Day 0)	Day 14 ± 5 days	M1 ± 7 days	D 45 ± 7 days	M3 ± 7 days	M4 / M5 ± 7 days	M6 ± 14 days	M9 ± 7 days	M12 ± 30 days	M18 ± 7 days	M24 ± 30 days / ET Visit
On-site visit ⊗ / telephone contact ☎**(1)**	⊗	⊗	⊗	☎	⊗	☎	☎	⊗	☎	⊗	☎	⊗
Informed consent	X											
Demographic information **(2)**	X											
Medical history **(3)**	X											
Laboratory tests **(4)**	X											
Prior and concomitant medications	X	X	X		X			X		X		X
Directed physical examination	X		X									X
Vessel mapping (if not done within 8 weeks)	X											
Inclusion/exclusion criteria	X	X										
Surgical placement of InnAVasc AVG		X										
Documentation of adjunctive procedures and any complications during surgery		X										
Adverse events **(5)**	X	X	X	X	X	X	X	X	X	X	X	X
InnAVasc Graft first use **(6)**		X										
Documentation of graft use and patency		X	X	X	X	X	X	X	X	X	X	X

Examination of access site			X		X			X		X		X
Documentation of graft interventions		X	X	X	X	X	X	X	X	X	X	X
Duplex ultrasound examination or angiography								X				
Patient-reported outcome questionnaires **(7)**	X		X		X			X		X		X

(1) Assessment Days and Months are relative to Day 0.

(2) Demographic data will also include smoking history.

(3) Medical history will include relevant prior and ongoing diseases, in particular: etiology of kidney disease and kidney transplant history, and risk factors.

(4) The following must be collected: CBC (platelets and hemoglobin), HbA1c, INR, pregnancy test (unless no childbearing potential).

(5) For screening, only AEs related to study specific procedures should be recorded.

(6) First use to be captured on D0. Reason for first use beyond 7 days will be documented in eCRF.

(7) In the event a patient early terminates due to no AVG placement or prior to first cannulation, this questionnaire is not required.

A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

Investigational Device: InnAVasc Vascular Access Graft

Protocol Number: CSP-1001

IDE Number: G180188

Addendum A: May 18, 2020

Sponsor

InnAVasc Medical, Inc.
110 Swift Avenue
Durham, NC 27705 USA

CONFIDENTIALITY STATEMENT

This protocol and all attachments are considered confidential information. The contents must not be disclosed, unless authorized in writing by InnAVasc Medical, Inc., except that this document may be disclosed to the appropriate Institutional Review Board (IRB) or duly authorized representatives of the competent authorities with similar requests for maintenance of confidentiality. All data and study results are similarly subjected to the same disclosure restrictions as the investigational plan, as stated above. All copies of this investigational device exemption remain the property of InnAVasc Medical, Inc.

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1. Background

The current study received IDE approval on September 7, 2018. A total of 26 subjects were enrolled in the study between January 2, 2019 and May 3, 2019, at which time enrollment in the study was concluded. As of the date of this addendum, 5 of the 26 treated subjects remain implanted with a functioning InnAVasc arteriovenous (IAVG). All of these subjects have completed follow-up through the one-year timepoint and are pending the 18-month follow-up timepoint.

The intent of this protocol addendum is to provide guidance to the investigators and research staff involved in this clinical investigation during the period of time clinical studies are being limited due to the national and international response to the COVID-19 pandemic. It is being implemented to ensure the safety of study subjects, maintain compliance with good clinical practice (GCP), and minimize risks to trial integrity during the COVID-19 public health emergency. This addendum is not intended to replace the policies and procedures specified by national, state, local or institutional authorities, but rather, to provide specific guidance on how to conduct this particular investigation in compliance with those requirements. This addendum is intended to remain in effect only for the duration of the public health emergency.

2. Study Objectives and Design

The study objectives and design of the original protocol will not be modified by this addendum.

The objective of this study is to evaluate the safety and effectiveness of the InnAVasc AVG for hemodialysis access in patients with ESRD. The safety and the effectiveness of the device and the procedure will be assessed using separate primary endpoints through 6 months.

This clinical trial is a prospective, multi-center, single-arm, non-randomized, premarket study designed to assess the safety and effectiveness of the InnAVasc AVG device in subjects with ERSD who require HD. The safety and effectiveness of the device will be evaluated with primary safety and effectiveness endpoints that will be summarized via standard descriptive statistics, including exact binomial 95% lower confidence intervals. No hypothesis tests are planned and there are no *a priori* study success criteria specified.

Data will be collected through 24 months.

3. Number of Subjects Affected

As of the date of this addendum, 5 of the 26 treated subjects remain implanted with a functioning IAVG. All other subjects with an abandoned IAVG have withdrawn from the study.

4. Number of Sites Affected

The five IAVG implanted subjects remaining in follow-up are enrolled at 3 of the original 5 study sites. The following sites are potentially impacted by this addendum:

- Site 14 (DIA) – 2 subjects
- Site 20 (Greenwood) – 2 subjects
- Site 19 (CTVS) – 1 subject

5. Study Duration

The original protocol defines that each subject will be followed for 24 months following implantation of the IAVG. As of the date of this addendum, the 5 remaining treated subjects have completed follow-up through the one-year timepoint, and are pending the 18-month follow-up timepoint.

Refer to Appendix 1 for the study visit schedule.

6. Study Procedures and Evaluations of Existing Subjects

All of the protocol-specified follow-up examinations require an in person visit by the subjects to the study site or a dialysis center. As such, if the study hospitals/clinics implement general restrictions on all patient visits, it is expected that these restrictions will also apply to the study-related follow-up visits. Nevertheless, it is still important to monitor the safety of the patients that have already been treated with the investigational device and to obtain as much of the protocol-defined efficacy data as possible.

For this reason, if hospital/clinic access restrictions are implemented due to the COVID-19 pandemic, the protocol-specified follow-up assessments are being reduced to include only those items that can be performed via a telephone call, and those requiring an in person visit by the patient are being temporarily suspended until such time as regular patient visits can be resumed. The details indicating which assessments are still required and which may be temporarily suspended for the remaining scheduled follow-up visits are described further below. **Importantly, InnAVasc and its clinical monitors will not require these temporarily suspended assessments or missing data (as prospectively specified in this addendum) to be reported as protocol deviations for GCP purposes. Rather, applicable follow-up written source documentation and case report forms (CRFs) should have a notation added indicating "certain assessments were not performed due to limitations imposed on in-person visits during the COVID-19 pandemic".**

Specific instructions as to how to conduct study follow-up visits and data collection **in the event of hospital/clinic access restrictions** are as follows:

6.1. 18 Month Follow-up Visit

The 18M follow-up visit evaluations are already scheduled to be performed via telephone. The required evaluations are as follows:

- Adverse events
- Documentation of InnAVasc Graft patency
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions

6.2. 24 Month Follow-up Visit

If hospital/clinic restrictions are implemented, the 24M follow-up visit evaluations should be

performed via telephone. The required evaluations are as follows:

- Concomitant medication
- Adverse events
- InnAVasc graft use for HD
- Documentation of InnAVasc graft interventions
- Patient-reported outcomes questionnaire

The following assessments will be temporarily suspended (unless these examinations are able to be performed at the dialysis center, and this this case, data will be collected as available):

- Physical examination
- Examination of access site

6.3. Additional Data Collection Instructions

6.3.1. Collection of HD session data from Dialysis Centers

Current practice for collection of HD session data from the Dialysis Centers is as follows:

- The Study Coordinator calls the Dialysis Center directly at regular intervals and verbally asks for the subject information needed. The information is recorded onto the appropriate source documents for data entry into the EDC.

6.3.2. Collection of HD Data from Homecare Sessions (if applicable)

In the event hospital/clinic restrictions are implemented and subjects begin undergoing remote HD sessions at home, the same data assessments pertaining to dialysis access use and performance of the IAVG will be performed. Study Coordinators will be expected to collect data via phone to the extent possible from the homecare personnel and record this onto the appropriate source documents.

6.3.3. Adverse Events

During the 18M or 24M follow-up visit phone call, the site's Study Coordinator should ask the subject directly whether they have experienced any adverse events since the prior follow-up, and if so, obtain sufficient information to allow the AE CRF to be completed. The questioning should include whether the most common expected adverse events (such as study graft thrombosis, infection, poor graft flow (stenosis), bleeding, hematoma, pseudoaneurysm, abandonment) have occurred or worsened. If a subject has a previous adverse event still ongoing since the last contact or that has resolved prior to the call, the Study Coordinator should obtain the necessary information to complete an updated AE CRF for those adverse event(s) as well.

6.3.4. Concomitant Medications

During the follow-up visit phone call, the Site Coordinator should ask the subject about current medications they are taking or have ceased taking and update the Conmed Log accordingly.

6.3.5. Questionnaires

The Patient Survey questionnaire (only one) can be conducted over the phone and transcribed by the site's Study Coordinator on the respective forms or mailed to the subject to complete and return. If transcribed, a notation should be written on the forms indicating this was done ("Transcribed by [initials and date]"). If the questionnaires are mailed to the patient, they should be sent just prior to the scheduled follow-up and the Site Coordinator should ensure they are completed and returned by the patient in a timely fashion.

6.3.6. Missed Visits

If follow-up telephone visits cannot be performed, this should be considered a missed visit and documented accordingly on the Visit CRF. If the missed visit is due to the patient contracting the COVID-19 virus, this should be specifically noted on the form.

6.3.7. Study Discontinuations

Any subjects that discontinue participation in the study due to COVID-19 should be clearly documented as a COVID-19 related discontinuation on the End of Study CRF.

7. Data Monitoring and Analysis

If planned on-site monitoring visits are no longer possible, InnAVasc will implement remote monitoring to the fullest extent possible to maintain oversight of the clinical sites and study data.

Prior to locking the database and InnAVasc will address in the statistical analysis plan how any protocol deviations or missing data related to COVID-19 will be handled for the prespecified analyses.

8. Appendix 1: Schedule of Assessments

Assessment	Screening/ Baseline (Day -45 to Day 0)	Treatment (Day 0)	Day 14 ± 5 days	M1 ± 7 days	D 45 ± 7 days	M3 ± 7 days	M4 / M5 ± 7 days	M6 ± 14 days	M9 ± 7 days	M12 ± 30 days	M18 ± 7 days	M24 ± 30 days / ET Visit
On-site visit ⊗ / telephone contact ☎**(1)**	⊗	⊗	⊗	☎	⊗	☎	☎	⊗	☎	⊗	☎	⊗
Informed consent	X											
Demographic information **(2)**	X											
Medical history **(3)**	X											
Laboratory tests **(4)**	X											
Prior and concomitant medications	X	X	X		X			X		X		X
Directed physical examination	X		X									X
Vessel mapping (if not done within 8 weeks)	X											
Inclusion/exclusion criteria	X	X										
Surgical placement of InnAVasc AVG		X										
Documentation of adjunctive procedures and any complications during surgery		X										
Adverse events **(5)**	X	X	X	X	X	X	X	X	X	X	X	X
InnAVasc Graft first use **(6)**		X										
Documentation of graft use and patency		X	X	X	X	X	X	X	X	X	X	X
Examination of access site			X		X			X		X		X

Documentation of graft interventions		X	X	X	X	X	X	X	X	X	X	X
Duplex ultrasound examination or angiography								X				
Patient-reported outcome questionnaires **(7)**	X		X		X			X		X		X

(1) Assessment Days and Months are relative to Day 0.
(2) Demographic data will also include smoking history.
(3) Medical history will include relevant prior and ongoing diseases, in particular: etiology of kidney disease and kidney transplant history, and risk factors.
(4) The following must be collected: CBC (platelets and hemoglobin), HbA1c, INR, pregnancy test (unless no childbearing potential).
(5) For screening, only AEs related to study specific procedures should be recorded.
(6) First use to be captured on D0. Reason for first use beyond 7 days will be documented in eCRF.
(7) In the event a patient early terminates due to no AVG placement or prior to first cannulation, this questionnaire is not required.

Investigational Plan
Addendum B

Title:	**A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease**
Protocol Number:	CSP-1001, Rev. B
IDE Number:	G180188
Sponsor:	InnAVasc Medical, Inc. 110 Swift Avenue Durham, NC 27705 USA
Primary Contact:	Shawn M. Gage, PA-C, Founder, Director of Clinical Operations InnAVasc Medical, Inc. 110 Swift Ave. Durham, NC 27705 shawn.gage@innavasc.com +1 919-452-4686
Date:	December 18, 2020

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1 BACKGROUND

The InnAVasc CSP-1001 study originally received IDE approval in November 2018. The Sponsor would now like to add a plan for longer-term follow-up of implanted subjects beyond the 24-month time point in the original protocol. This addendum describes the planned assessments, duration of follow-up, and safety reporting that will be performed for the longer-term follow-up (Section 2.4.2).

2 OVERALL STUDY DESIGN AND PLAN

The objective of this study is to evaluate the safety and effectiveness of the InnAVasc AVG for hemodialysis access in patients with ESRD. The safety and the effectiveness of the device and the procedure will be assessed using separate primary endpoints through 6 months.

This clinical trial is a prospective, multi-center, single-arm study designed to assess the safety and effectiveness of the InnAVasc AVG device in subjects with ESRD who require HD. The study population included 26 enrolled subjects, male and female, who are appropriate candidates for implantation of an InnAVasc AVG and require hemodialysis treatment for ESRD. The safety and effectiveness of the device will be evaluated with primary safety and effectiveness endpoints that will be summarized via standard summary statistics, including 95% two-sided confidence intervals. No hypothesis tests are planned for the primary study endpoints and there are no *a priori* study success criteria specified.

The total follow-up for the original protocol included up to 24 months. The long-term follow up described in this addendum will continue to 5 years (60 months).

2.1 Study Population and Inclusion-Exclusion Criteria

The study population intended for enrollment and the Inclusion/Exclusion criteria for subjects will remain the same as defined in the original protocol.

2.2 Number of Sites

Up to 10 investigational sites in the United States.

2.3 Number of Patients

26 subjects were enrolled in the study.

2.4 Study Duration

2.4.1 Original Protocol Study End Point Duration

The original protocol defines that each subject will be followed for 24 months following the index surgical implant procedure, or until lost to follow up or study device abandonment. The primary analysis will occur when all subjects reach the month 6 follow up assessment.

All procedures, evaluations, and collection and documentation of clinical data will remain the same as defined by the original protocol and are designed to provide the data necessary to assess the study time points and document any adverse effects related to device use. Definitions of expected adverse events reported during the original protocol study duration will remain the same as defined in the original protocol.

2.4.2 Additional Long-Term Follow-up

2.4.2.1 Long-Term Follow-up Duration

This addendum is defining longer term subject follow-up as an addition to the original protocol. These additional visits are intended to provide for subject follow-up through a total of 5 years (60 months) following the procedure.

Subjects will be followed at an additional eight (8) study time points: 27, 30, 33, 36, 42, 48, 54, and 60 months following the procedure. Months 27, 30, 33, 42, and 54 will be subject phone contact assessments and Months 36, 48, and 60 will be in-person clinic assessments by the study PI/research staff.

2.4.2.2 Long-Term Follow-up Assessments

Evaluations, and collection and documentation of clinical data for the additional long-term follow-up visits will be performed as described below. The phone assessments will include study graft patency and use, cannulation-related issues, anticoagulant/antiplatelet medications and device or HD-related adverse events. The in-person clinic assessments will capture access site exam and duplex ultrasound of the study graft site, and a patient reported outcomes survey, in addition to those assessments captured in the phone assessments.

Phone Assessments (Months 27, 30, 33, 42 and 54)

- Assessment of InnAVasc graft patency and function for hemodialysis;
- Assessment of and documentation of study graft related AEs since the last call/assessment;
  - HD procedure or study graft-related AEs, as well as any interventions performed on the study graft.
  - Study graft abandonment and/or explantation.
- InnAVasc graft cannulation-related issues;
- Antiplatelet and anticoagulant medications will be documented.

In-person Clinic Visits (Months 36, 48, 60)

- Assessment of InnAVasc graft patency and function for hemodialysis;
- Assessment of and documentation of study graft related AEs since the last call/assessment;
  - HD procedure or study graft-related AEs, as well as any interventions performed on the study graft.
  - Study graft abandonment and/or explantation.
- InnAVasc graft cannulation-related issues;
- Antiplatelet and anticoagulant medications will be documented.
- Examination of InnAVasc graft access site;
- Duplex ultrasound examination (confirmation of study graft function and patency, flow, and monitoring of entire graft length for aneurysm development);
- Patient reported outcomes questionnaire (SF-VAQ).

Table 1 below describes the additional long –term visits as described above that will occur during years 3-5 of patient follow-up in the study for each visit timepoint.

Table 1: **Extended Follow-Up Schedule of Assessments**

	Year 3				Year 4		Year 5	
	M27 ± 14 days	**M30 ± 14 days**	**M33 ± 14 days**	**M36 ± 14 days**	**M42 ± 21 days**	**M48 ± 30 days**	**M54 ± 21 days**	**M60 ± 30 days**
Assessments	**Phone**	**Phone**	**Phone**	**Clinic**	**Phone**	**Clinic**	**Phone**	**Clinic**
Assessment of Study Graft Patency & Function	X	X	X	X	X	X	X	X
Adverse Events (device & HD specific)	X	X	X	X	X	X	X	X
Study Graft Cannulation Issues	X	X	X	X	X	X	X	X
Antiplatelet/Anticoagulant Medications	X	X	X	X	X	X	X	X
Examination of Study Graft Access Site				X		X		X
Duplex Ultrasound Examination				X		X		X
Patient-Reported Outcome Questionnaire				X		X		X

2.4.2.3 Long-Term Follow-up Adverse Event Reporting

Adverse events that will be collected at the additional long-term follow-up visits will be limited to just those events that are related to the InnAVasc AVG, or are related to HD procedures in general. Examples of such events are further defined as follows:

Device Related AE

An adverse event that is deemed a device related event or hemodialysis therapy related event (procedure of placing the dialysis needles into the study graft) may be defined as follows (note: these definitions are the same as defined in the original protocol):

- Missed graft puncture attempt
- Hematoma formation (during HD, or post needle withdraw)
- Infiltration of access site (ecchymosis, or swelling)
- Identification of Pseudoaneurysm development
- Bleeding from graft (> 10 min)
- Uncontrollable bleeding
- Localized Infection present at access site
- Systemic Infection (suspected to be related to the study device)
- Ulcers of the skin or eschar development overlying the study device
- Skin erosion over the study device
- Suspected backwall puncture
- Elevated pressures in graft circuit
- Stenosis of the study graft (includes a. and v. anastomoses and intragraft, but NOT inflow or outflow lesions)
- Kinking or twisting of the study device
- Needle displacement during dialysis
- Wounds or complications at the access site
- Seroma or fluid collection around the study device
- Thrombosis of the study graft

HD Procedure Related AE

An adverse event that is related to the HD procedure in general will also be reported, regardless of whether the event is considered to be device or therapy-related or not. An adverse event that is deemed a HD therapy-related event may be defined as follows:

- Missed graft puncture attempt
- Hematoma formation (during HD, or post needle withdraw)
- Infiltration of access site (ecchymosis, or swelling)
- Bleeding from graft (> 10 min)
- Uncontrollable bleeding
- Localized Infection present at access site
- Ulcers of the skin or eschar development overlying the study device
- Skin erosion over the study device
- Suspected backwall puncture
- Elevated pressures in graft circuit
- Needle displacement during dialysis
- Wounds or complications at the access site
- Seroma or fluid collection around the study device
- Thrombosis of the study graft

Serious adverse event (SAE) and unanticipated and serious adverse device effect (USADE) reporting and adjudication will continue to be performed as defined in the original protocol.

All other aspects of the clinical trial and protocol not addressed by this addendum will remain the same as defined in the original study protocol.

RESEARCH SUBJECT CONSENT FORM AND HIPAA AUTHORIZATION

TITLE: A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

PROTOCOL NO.: CSP-1001
IRB Protocol#: 420180414

SPONSOR: InnAVasc Medical, Inc.
110 Swift Ave.
Durham, NC 27705

<<CF-Main Header Block - Investigator>>
STUDY RELATED PHONE NUMBER(S): <<CF-Main User Defined #1>>

You are being invited to take part in this research study because you have kidney failure and are currently undergoing hemodialysis (a process to filter your blood) or are expected to require hemodialysis within 60 days. To continue with long-term hemodialysis, it is generally considered best practice to create a permanent route to connect your blood stream to the dialysis machine. There are several ways to do this including surgically implanting an arteriovenous graft (AVG), a short piece of plastic-like tubing, to connect an artery to a vein, or by surgically making a direct connection between your artery and vein (this connection is called an autologous arteriovenous fistula or AVF). Your doctor will have already explained why he or she thinks that a graft or an AVF is the right approach for you. If you are being considered for this study, it has been determined that an AVG is your best option and that you are not, or you are no longer, an AVF candidate. A person who takes part in a research study is called a research subject, or research participant.

WHAT SHOULD I KNOW ABOUT THIS RESEARCH?
Someone will explain this research to you.

- This form sums up that explanation. Please read this consent form carefully and take your time making your decision as to whether to participate.
- Taking part in this research is voluntary. Whether you take part is up to you.
- You can choose not to take part. There will be no penalty or loss of benefits to which you are otherwise entitled.
- You can agree to take part and later change your mind. There will be no penalty or loss of benefits to which you are otherwise entitled.
- If you don't understand something, ask questions.
- Ask all the questions you want and be sure they are answered before you decide.
- Before you decide, we encourage you to talk to anyone you feel comfortable with. If you would like, you may take this consent form home with you to discuss with your friends and family before you decide whether to participate in this study.

This study is sponsored by InnAVasc which is paying the study doctor, the hospital, or the clinic, to conduct the study. If applicable, the study doctor will tell you about any financial interests he or she may have in InnAVasc. <<CF-Main Financial Disclosure>>

WHY IS THIS RESEARCH BEING DONE?
The purpose of this research is to assess the safety and effectiveness of a new investigational dialysis graft developed by InnAVasc.

The InnAVasc Graft is made from the same materials as standard grafts, but with added medically safe materials that may make the graft easier to identify, safer to stick for dialysis, more durable, and less likely to bleed after your dialysis session when

compared to standard grafts. The InnAVasc graft is an investigational product, which means that this is not yet approved by government agencies like the FDA, but preliminary tests in the laboratory and in animals have proven safe enough to be allowed to be used in human clinical studies such as this.

At least 60 subjects will take part in this research at approximately 6 different medical facilities/hospitals in the United States. This will be the first time the InnAVasc graft will be used in human subjects.

HOW LONG WILL I BE IN THIS RESEARCH?
The total length of your involvement in the study will be up to 5 years (60 months). You will continue in the study as long as your graft is still open and flowing, or working for dialysis. Follow up assessments will become fewer and further apart as the study goes on. After 2 years, five of the follow-up assessments will be by telephone, three will be at your study doctor's office.

WHAT HAPPENS TO ME IF I AGREE TO TAKE PART IN THIS RESEARCH?
If you agree to take part in the study, you will be asked to sign and date this consent form. You will then have several tests and procedures done to ensure you are eligible for the study (this is called screening). You will be asked to complete a short survey regarding your current and previous dialysis access.

After completing the screening visit, your study doctor, physician assistant (PA), or other authorized study personnel will review your test results and talk with you. If you are eligible for the study, you will be scheduled for surgery.

During the study you will be asked to come to the study doctor's office for regular study visits. As a part of these visits, the study doctor will obtain information about you and your InnAVasc graft from other healthcare personnel and people from dialysis centers looking after you. During months that an in-person study visit is not scheduled, you will have telephone contact with your study coordinator to answer a few simple questions about your study graft. Study visits will become less frequent over time.

During the visits, you will have several tests; some of these would have been done as a part of your regular care and some are done as part of this investigational study.

<u>The Day of Surgery</u>
If you qualify to take part in the research study, surgery will be scheduled within 45 days of your screening visit.

All participants will be treated the same: all subjects will receive the InnAVasc Graft and the surgery for implementation of the graft will be similar for all subjects.

On the day of surgery, you will have an InnAVasc graft surgically implanted in your upper arm or forearm just under the skin and attached to your own artery and vein (just like a standard-of-care graft). This treatment will provide an intended permanent route to receive hemodialysis in the same fashion as a standard of care graft. Within 7 days after surgery, needles used for your dialysis access will then be inserted into the InnAVasc graft through your skin, as long as your doctor agrees that it is appropriate.

The surgery may be carried out under general or local anesthesia. During or immediately after surgery your study doctor will check that the graft is working properly, and that blood is flowing through the access.

Follow-up Visits

You will be asked to come to the study doctor's office for eight study visits following your surgery so that your InnAVasc Graft can be checked, and an additional five follow up assessment telephone calls over the final 3 years of the study. The first study visit will be approximately 2 weeks after the implant surgery, which should correlate with the standard post-operative visit that your doctor will schedule. Additional in person visits will occur at approximately 45 days, and 6, 12, 24, 36, 48, and 60 months after surgery. At these study visits, you will be asked to complete a short, 12 question survey about your dialysis access. This will be the same survey completed at the screening visit. If needed, a physical exam will be performed. Telephone contact will be made with you and your dialysis unit charge nurse during the months listed below when you do not have an in-person study visit to check on you and the status of the graft. Formal telephone contact will be made with you at approximately 27, 30, 33, 42, and 54 months after surgery to ask about InnAVasc graft function and any potential problems with dialysis.

At all visits, in your doctor's office or by phone, it is very important that you tell your study doctor (or other study personnel) about any problems you experience or about any change in medications. It is especially important to mention any procedures that have been done to your InnAVasc Graft.

The table below lists what tests and procedures will be performed at each of your study visits.

Visit	Description of Study-related Tests/Procedures Performed During Study Visits
Screening Visit	• Your study doctor will collect your medical history and ask you about any medications you are currently taking. • A physical exam will be conducted. • A small amount of blood (approximately 2 tablespoons or 30 mL) may be collected to do

	several tests. • An ultrasound may be done to check that you have suitable blood vessels for the surgery, if it hasn't been done within 8 weeks previously. An ultrasound is a test that uses sound waves to make an image of the inside of your body. This is typical before most AV access surgeries. • Completion of dialysis access survey.
Day of Surgery	• InnAVasc Graft implant surgery (no different than surgery to implant a standard dialysis graft). • During or immediately after the surgery, your study doctor will check that your InnAVasc AVG is working properly.
In Office Follow-Up Visits	• You will be asked to come into the office for assessments on the following days after surgery: 14 days, 45 days, 3 months, 6 months, 12 months, 24 months, 36 months, 48 months, and 60 months. The following assessments and procedures will be performed at the scheduled follow-up visits/assessments: • Your study doctor will ask you questions about how you and your InnAVasc AVG are doing. • He/she will look at your InnAVasc AVG and will ask about any problems you might be having. • During these study visits you may have a physical exam. • At the 6-month, 36-month, 48-month, and 60-month visits, an ultrasound (takes a picture with sound waves) will be done on the InnAVasc AVG to check that it is working properly. • At each visit, your study doctor will ask if your InnAVasc AVG is being used for hemodialysis. • Completion of dialysis access survey. • Study personnel will contact your dialysis unit to check to see if you have had any problems with your InnAVasc AVG or if you have had any procedures performed on your graft up to month 24 only..
Telephone Follow up	• At months 1, 3, 4, 5, 9, and 18, study personnel will contact you and your dialysis unit to check to see if

	you have had any problems with your InnAVasc AVG or if you have had any procedures performed on your graft. You will be asked to participate in additional assessments by phone after the first 24 months at the following time points: 27, 30, 33, 42, and 54 months after surgery. The following assessments will be performed at the scheduled follow-up visits/assessments: • You will be asked about new medications or changes in current medications you are taking. • You will be asked if your InnAVasc Arteriovenous Graft is still working, if you are using it for hemodialysis and if you have had any problems or had any procedures performed on it. You will also be asked about your general health overall.

Dialysis using the InnAVasc AVG

Your study doctor will decide when the InnAVasc AVG is ready to be used for dialysis for the first time. Since the InnAVasc AVG is an immediate use graft, it may be used for the first time as early as the day of implant depending on the opinion of your study doctor. The graft may be able to be used for hemodialysis much sooner than standard grafts due to the materials used and unique construction of the graft. The procedures for dialysis with the InnAVasc Graft are the same as for a standard graft, but we anticipate easier cannulation and less bleeding after dialysis. Your usual dialysis unit will be educated on the use of InnAVasc AVG prior to your first session, but we will also give you a reminder bracelet and informational card that will provide instructions for use in case you go to a different hemodialysis unit. Information from your dialysis center will be collected for study purposes. The data collected from your dialysis center will be part of your routine care and include laboratory data drawn at the dialysis center, data about any procedures/interventions done at your dialysis center and data from your dialysis machine.

Keeping Discarded Parts of the InnAVasc AVG

In some cases, during a possible surgery to revise the InnAVasc AVG if necessary, a small part of it may have to be removed and would normally be discarded. InnAVasc would like to use that discarded piece of the InnAVasc AVG to conduct special tests that would tell us how your tissue reacts to the InnAVasc AVG and how the graft looks following several dialysis needle cannulations. You do not need to agree to this to be part of the study; we ask that you indicate your choice about this separately from the main agreement to join the study at the end of this form.

WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?
If you take part in this research, you will be responsible to:

- Follow the instructions you are given by the study doctor, PA or other study staff; in particular, follow your surgeon's instructions for the maintenance of wound dressings and any medications that the surgeon may prescribe.
- Provide the cannulation instructions for use to anyone new to cannulation of your InnAVasc graft. The instructions can be viewed by scanning a QR code link on the reminder band and information card provided to you. You must carry one of these items with you at all times to ensure proper use of your InnAVasc graft at each dialysis session.
- Report to your surgeon/the study doctor or other study staff after discharge and at every study visit, immediately any changes in your health such as sudden increase in pain, redness, wound drainage or excessive local swelling or bruising around the operative site, or any generalized swelling of the operative arm. Note that all wounds, however created, share some risk of infection, bleeding and poor wound healing.
- Follow your surgeon's instructions regarding what types and degrees of activity are to be avoided at various times postoperatively.
- Return to your surgeon's office/research study center as scheduled for your postoperative visits.
- Tell the study doctor or staff if you want to stop being in the research study.

COULD BEING IN THIS RESEARCH HURT ME?
In general, the type of risks associated with having the InnAVasc AVG implanted are expected to be like the risks of having a standard dialysis graft surgery. You will be asked to sign a separate consent form at the place of your surgery for the actual surgical procedure.

Known Risks of Arteriovenous Graft Implantation:

Event Category	Event (Medical)	Event (Lay)
Bleeding	Early, postoperative	
	Prolonged bleeding from needle puncture site	
Infection	Early infection, during procedure	Infection related to surgery
	Late infection, due to cannulation	Needle stick site infection
Noninfectious fluid collections	Hematoma	Collection of blood under skin

	Seroma	Fluid collection
	Lymphocele	Lymphatic fluid collection
Anastomotic complications	Hemorrhage	Bleeding
	Pseudoaneurysm	Outpouching (sac) of contained blood
	Stenosis with intimal hyperplasia	Narrowing of the area where the graft is sewn to blood vessel
Mid-AV access/runoff vein complications	Dilation/aneurysm	
	Pseudoaneurysm at needle stick site	Outpouching (sac) of contained blood at the needle stick site
	Mid-AV access stenosis	Narrowing in the middle of the graft (at needle stick sites)
AV access malfunction	Insufficient inflow	Poor flow into the graft
	Insufficient runoff	Poor flow out of the graft
	Inability to puncture	Not able to stick graft
Ischemia	Steal syndrome	Too much blood flow into the graft and not enough to the hand
Cardiac	Myocardial infarction	Heart attack
	Congestive heart failure	Heart can't pump very well and gets overloaded with blood
	Arrhythmia	Abnormal heart rhythm
	Valve disorders; stenosis and insufficiency	Heart valve malfunction
	Hypertension	High blood pressure
	Hypotension	Low blood pressure
Wound	Wound infection	
	Wound pain	
	Wound dehiscence	Wound separates
	Serous wound drainage	Fluid drainage
	Lymphorrhea	Draining lymphatic fluid
	Hematoma	Collection of blood in the wound
	Ecchymosis	Bruising
Venous	Deep venous thrombosis	Clot in a large vein (typically the leg)
	Pulmonary embolism	Clot (from a vein) that travels to the lung
	Paradoxical embolization	Multiple clots
	Venous hypertension	High pressure in the vein
Local	Arm edema	Swelling of the whole arm
	Arm pain	

	Back pain	
Cerebrovascular	Transient ischemic attack	“mini” (temporary) stroke
	Stroke	Lack of blood flow to a portion of the brain “brain attack”
	Intracranial hemorrhage	Bleeding into the brain
Genitourinary	Urinary retention	Unable to pee
	Urinary tract infection	Infection of the bladder
	Renal stones	Small mineral based stones in the kidneys
	Renal insufficiency, failure	Kidney failure
	Hematuria	Blood in the urine
	Impotence and other disorders of sexual function	Unable to get an erection
Pulmonary	Exacerbation of chronic lung disease	Making a lung disease worse
	Pneumonia	Infection of the lungs
	Pulmonary embolism	Clot (from a vein) that travels to the lung
	Respiratory failure	Lung failure (unable to breath)
	Bronchitis	Inflammation of the small tubes of the lungs
	Bronchospasm	Spasm/constriction of the tubes in the lungs
Gastrointestinal	Peptic ulcer disease	Stomach ulcer
	Reflux esophagitis	Inflammation of the tube that food passes through
	Nausea and vomiting	
	Diarrhea	
	Constipation	Unable to have a bowel movement for more than 3 days
	Hepatitis	Infection/inflammation of the liver
	Hepatic insufficiency	Poor liver function
	Cholelithiasis / cholecystitis	Stones in the or inflammation of the gall bladder
Metabolic/systemic disorders	Electrolyte imbalances	
	Hyperglycemia	High blood sugar
	Hypoglycemia	Low blood sugar
	Fluid overload	
	Dehydration	Not enough fluid or water in the

		body
	Thrombocytopenia	Low platelet count
	Leukopenia	Low white blood cell count
	Anemia with or without need for transfusion	Low red blood cell count/concentration
Miscellaneous	Sepsis	Blood infection that can lead to organ failure and/or death
	Skin erosion	
	Compartment syndromes	Increased pressure in a muscle compartment
	Psychiatric disorders including depression	
	Mental status changes	
	Insomnia	Not able to sleep
	Allergic reactions to device components	Allergic reaction to the graft
	Allergic reactions to concomitant medications	Allergic reactions to medicines you may be taking or have been administered

Careful and frequent monitoring of the InnAVasc AVG by physical assessment and telephone contact is expected to detect problems that may occur. The risks with any dialysis access include the following typical events, most of which can be reversed by careful medical care or an operation:

- Dilation (pseudoaneurysm) or weakening of the access; rarely a dilation may burst
- Bleeding after surgery or from the graft after dialysis; possible hematoma formation (collection of blood under the skin)
- Blockage (clotting) of the access
- Narrowing (stenosis) of the access
- Infection around or in the access
- Skin ulcers (skin erosion) Fluid collection (seroma)
- Discomfort or swelling in the arm or hand
- Steal syndrome (blood flow in the wrong direction caused by unnatural connection of blood vessels)

Any of these problems may require additional tests, such as ultrasound or blood tests, to help identify the cause. Sometimes further surgery is needed. If you or the nurses at the dialysis center believe the InnAVasc AVG has become blocked, you should make sure that your study doctor (or nurse) is told about this urgently.

In this current study, we have seen a higher frequency of blockage (clotting) of the access and removal of the study graft as compared to the frequency of a standard dialysis graft. For this reason, additional enrollment in the study has been halted until more information is known. Subjects who are currently enrolled and have a working InnAVasc AVG may continue in the study and use the graft as usual.

In addition, it is possible that there might be InnAVasc AVG risks that we do not know about. If new information becomes available that could affect your health or welfare or willingness to stay in this study, we will tell you about that as soon as possible.

If your InnAVasc AVG stops working, another access for hemodialysis will need to be created or implanted/placed. Any surgery to do this is not a part of this study.

Risks of Anesthesia

The InnAVasc AVG will be placed/created surgically under either general anesthesia (you are given special drugs to make you sleep during your operation) or local anesthesia (you are given special drugs that numb the arm that the InnAVasc AVG is being placed in). Your doctor will decide which is best for you after talking with you. Anesthesia has some risks that may include: nausea (feeling sick), vomiting, heart attack, a reaction to the medicines given, stroke, and death. You will be asked to sign a separate consent form at the place of your surgery for the use of anesthesia during your surgery.

Risks of Drawing Blood

You may feel a sharp prick when the needle is pushed through the skin and there may be bruising around the puncture site. Infection, bleeding, or fainting are possible, although unlikely. In rare cases taking blood samples may cause nerve damage at the needle puncture site.

Risks of Ultrasound Scan

Ultrasound scanning is a non-invasive pain-free method use sound waves to make an image of the inside of your body. This examination is carried out by placing a small device on the skin surface and moving it along the blood vessels. To improve the contact with the skin special gel may be used. In rare cases this gel may cause skin irritation. During scanning, you must remain still.

In addition to these risks, taking part in this research may harm you in unknown ways.

Pregnancy

If you are female and become pregnant during the study, please tell your study doctor who will discuss the situation with you and keep a careful watch over you. Currently, there has been no experience of women becoming pregnant while they are using the InnAVasc AVG. This study may involve risks to the fetus that are not yet known,

although it is unlikely, given these materials have all been used safely in humans before.

If you are male, you do not need to tell the study doctors or nurses about any pregnancies of your partner.

WILL IT COST ME MONEY TO TAKE PART IN THIS RESEARCH?
There will be no additional costs to you because of being in this study. InnAVasc will provide the InnAVasc AVG free of charge and will pay for tests that are not a part of your routine medical care. Routine medical care (care you would have received if you were not in the study) will not be covered by InnAVasc. The surgical procedure to implant the InnAVasc AVG is considered routine medical care and will not be covered by InnAVasc. InnAVasc will cover additional costs for things that are not considered part of your routine medical care that occur because you participate in this study.

You should also note that insurance or other reimbursement mechanisms might not fund the medical care you receive because you are participating in a clinical investigation even when the care is the standard care you would otherwise receive if not participating in a clinical investigation. You should discuss this with your study doctor (or nurse) or with anyone involved in paying for your medical care.

WILL BEING IN THIS RESEARCH BENEFIT ME?
The main reason for you to participate in this study is to add knowledge about the use of InnAVasc AVG for hemodialysis rather than to improve your current state of healthcare delivery.

We cannot promise any benefits to you or others from your taking part in this research. However, the InnAVasc Graft was developed with the goal to make it easier to identify and stick your graft, to protect patients from needle related injuries (for example, back wall or side wall injuries that cause excessive bleeding), and to reduce bleeding after dialysis.

It is possible that the InnAVasc AVG may provide better outcomes compared to a standard AVG, but that is not yet known or confirmed. However, the information collected in this study may help other patients in the future.

WHAT OTHER CHOICES DO I HAVE BESIDES TAKING PART IN THIS RESEARCH?
If you do not want to join the study, your doctor will discuss with you the best dialysis access for you and how your dialysis will be managed in the future. The types of risks associated with alternative dialysis accesses are expected to be like those you might experience if you will join this trial. However, because the InnAVasc AVG is an

investigational product, it is not known how the risks of other dialysis accesses compare to the InnAVasc AVG.

Alternative methods of renal replacement therapy include peritoneal dialysis (fluid exchange in your belly), or kidney transplant. It is always advisable to ask your nephrologist or surgeon if you are a candidate for these other forms of kidney replacement therapy.

WHAT HAPPENS TO THE INFORMATION COLLECTED FOR THIS RESEARCH?
Federal regulations give you certain rights related to your health information. These include the right to know who will receive the information and how it will be used. The study doctor must obtain your authorization (permission) to use or release any health information that might identify you.

What information may be used and shared?
The study doctor and study staff will use and share your health information as part of this research study. Except when required by law, you will not be identified by name, address, telephone number or other facts that could identify the health information as yours.

Examples of the information that may be used are:

- Medical records (from any doctor, hospital or other healthcare provider)
- Information created or collected during the research. This could include your medical history, and dates or results from any physical exams, laboratory tests or other tests.

Information about how you and your InnAVasc AVG are doing will be kept in special study records with security protections. If you choose to participate in the study, these records will be entered into a computerized, secure database.

Who will receive information about me?
The study doctor and study staff will share your personal health information with:

- The research Sponsor
- People who work with the research sponsor
- The Institutional Review Board (IRB) that reviewed this research. The IRB is a group of scientists and non-scientists who review the ethics of research. The goal of the IRB is to protect the rights and welfare of study subjects.<<CF-Main SMO Company 1>><<CF-Main Affiliated IN Language 1>>
- Government agencies, such as the Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Other regulatory agencies

Why will this information be used and/or given to others?
The sponsor and the groups above will use your health information:

- to complete this research
- to evaluate the results of the study
- to check that the study is being done properly
- to obtain marketing approval for new products resulting from this research

Is my health information protected after it has been given to others?
Your health information may be further shared by the groups above. If shared by them, the information will no longer be covered by this Authorization. These groups are committed to keeping your health information confidential.

What if I decide not to allow the use of my health information?
You do not have to sign this form. If you do not sign this form, you cannot take part in this research study.

May I withdraw or revoke (cancel) my permission?
YES. You may withdraw your permission to use and disclose your health information at any time. You can do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in the research study.

What happens if I want to withdraw my authorization?
Information that has already been gathered may still be used and given to others. If you withdraw your permission, no new health information will be gathered unless you have a side effect related to the study.

If you withdraw from the study but do not withdraw your Authorization, new health information may be collected until this study ends.

Will my authorization expire?
If you do not withdraw this Authorization, it will remain in effect.

If the research site is located in California, Delaware, Indiana, Washington, or Wisconsin this authorization will expire on 31Dec2060.

There is no expiration of this authorization except for research conducted in the states listed above.

May I review or copy the information obtained or created about me?
YES. You have the right to review and copy your health information. However, your access to this information may be delayed until the study is complete.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

During one or more of your visits, a representative from the Sponsor may be present to observe the surgery or other procedures and provide information to the study doctor. Your privacy will be protected if one or more of these individuals are present.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete confidentiality.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data or specimens collected in this research might be deidentified and used for future research or distributed to another investigator for future research without your consent.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS RESEARCH?
If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at (888)-303-2224 or (800) 562-4789, irb@cgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

WHAT IF I AM INJURED BECAUSE OF TAKING PART IN THIS RESEARCH?
If you are hurt or get sick in the study, you should call the study doctor. The study doctor will make sure you get medical care for your injury or illness. If you experience any injury as a direct result of your participation in this research study, immediate treatment will be provided. InnAVasc will pay only for treatment related to problems that occur as a direct result of the study provided all aspects of the study protocol have been followed correctly.

The study doctor/site has no program for financial compensation for injuries which you may incur as a result of participation in this research. The costs of the treatment may be covered by the study site, InnAVasc, or billed to you or your insurer just like other medical costs, depending on several factors. However, you are not prohibited from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research, including the study site.

If InnAVasc covers these costs they will need to know some information about you like your name, date of birth, and Medicare Health Insurance Claim Number, or, if you do not have one, your Social Security Number. This information will be used to check to see if you receive Medicare, and, if you do, report the payment they make to Medicare. InnAVasc will not use this information for any other purpose.

CAN I BE REMOVED FROM THIS RESEARCH WITHOUT MY APPROVAL?
The person in charge of this research can remove you from this research without your approval. Possible reasons for removal include:

- It is in your best interest regarding your health and well-being
- You have serious problems
- New information indicates that the InnAVasc AVG poses a significant risk to you
- You become pregnant
- The research is canceled by the FDA or the sponsor
- You are unable to keep your scheduled appointments
- You are unable or unwilling to fulfill the study requirements

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

WHAT HAPPENS IF I AGREE TO BE IN THIS RESEARCH, BUT I CHANGE MY MIND LATER?
Joining this study is completely voluntary; you may choose to join the study and then decide to stop coming for visits. If you choose to stop coming for visits or decide not to participate there will be no penalties or loss of other benefits you would otherwise be entitled to receive.

If you agree to be in the study, even if your InnAVasc AVG stops working, you will be asked to attend the study visits during the first 6 months. You can choose to stop coming for study visits at any time without affecting the way you are looked after. Before you make that decision, please talk with your study doctors or nurses, so we can assure a safe and orderly withdrawal. If you do decide to stop coming for study visits, we would like to be able to contact your doctors or nurses to understand how you and your

InnAVasc AVG are doing; we will ask you to indicate your choice about this separately from agreeing to be in the main study at the end of this form.

If you decide to stop coming for study visits, the InnAVasc AVG will stay in your arm and be used for dialysis as long as it continues to work. InnAVasc may retain and use any research results that have already been collected before you decide to stop coming to study visits. InnAVasc must do this to comply with its legal obligations and to maintain the quality of the study.

If new information becomes available that could affect your health or welfare, or willingness to stay in the study, we will tell you about that as soon as possible.

WILL I BE PAID FOR TAKING PART IN THIS RESEARCH?
You will receive $XX per study visit that you attend in person to cover the costs related to you coming for a study visit; this will cover things like travel and parking, and $20 per phone follow up visit to cover your time. In addition, you should discuss with your study doctor (or nurse) whether arrangements can be made to make your visits to the office easier.

<<CF-Main Payment for Part. Paragraph>>

WHO HAS REVIEWED THIS STUDY?
This study has been reviewed by an Independent Review Board (IRB) which is a committee whose task it is to protect patients from harm.

STATEMENT OF CONSENT:

A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

1. I confirm that I have read and understand the informed consent form for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without affecting my medical care or legal rights. ☐
3. I will be given a copy of this signed information sheet and consent form to keep for myself<<CF-Main User Defined #2>>. ☐
4. I understand that my medical notes and information collected during the study may be looked at by individuals from InnAVasc and its representatives, from government agencies (FDA) or from the hospital / clinic, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
5. I consent to the transfer of my personal information to other countries, I understand that reasonable steps will be undertaken to ensure my confidentiality. ☐

By signing below (and also initialing tick boxes by statements above), I am agreeing to participate in this research study, but understand that I can change my mind at any time.

Your signature documents your consent to take part in this research and to allow the use or disclosure of your health information.

Printed Name of Adult Subject Capable of Consent		
Signature of Adult Subject Capable of Consent		Date

I confirm that I have explained the study to

_____ and that he/she understands what his/her participation in the study entails and the risks involved. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Printed Name of Person Obtaining Informed Consent	
Signature of Person Obtaining Consent	Date

CONSENT TO ALLOW THE STUDY DOCTOR TO FOLLOW-UP WITH MY HEALTH CARE PROVIDERS IN THE EVENT I DECIDE TO STOP ATTENDING STUDY VISITS

A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

By signing below, I am agreeing that if I choose to stop coming for visits to the study doctor's office, the study doctor, or nurse can get information on how I am doing and whether my InnAVasc AVG is working properly. To do that, the study doctor may contact my doctor, or dialysis center.

I understand that I do not have to agree to this to be part of the main research study. I am agreeing to participate in this part of this research study but understand that I can change my mind at any time.

Printed Name of Adult Subject Capable of Consent	
Signature of Adult Subject Capable of Consent	Date

I confirm that I have explained this aspect of the study to

_____ and that he/she understands what his/her participation in the study entails and the risks involved. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Printed Name of Person Obtaining Informed Consent	
Signature of Person Obtaining Consent	Date

CONSENT TO ALLOW FOR THE STUDY DOCTORS TO COLLECT ANY DISCARDED PARTS OF THE INNAVASC AVG

A Study to Evaluate the Safety and Effectiveness of the InnAVasc Arteriovenous Graft for Hemodialysis Access in Patients with End-Stage Renal Disease

I understand that any problems associated with the InnAVasc AVG may require extra surgery.

I agree that any part of the InnAVasc AVG removed during surgery may be sent to InnAVasc or its designee for special testing.

I understand that this sample will be stored and will not be returned to me.

I understand that I do not have to agree to this to be part of the main research study. I am agreeing to participate in this part of this research study but understand that I can change my mind at any time.

Printed Name of Adult Subject Capable of Consent	
Signature of Adult Subject Capable of Consent	Date

I confirm that I have explained this aspect of the study to

_____ and that he/she understands what his/her participation in the study entails and the risks involved. I further attest that all questions asked by the subject were answered to the best of my knowledge.

Printed Name of Person Obtaining Informed Consent	
Signature of Person Obtaining Consent	Date

<<CF-Main User Defined #9>>

CALIFORNIA HIPAA AUTHORIZATION

Federal regulations give you certain rights related to your health information. These include the right to know who will receive the information and how it will be used. The study doctor must obtain your authorization (permission) to use or release any health information that might identify you.

What information may be used and shared?
The study doctor and study staff will use and share your health information as part of this research study. Except when required by law, you will not be identified by name, address, telephone number or other facts that could identify the health information as yours.

Examples of the information that may be used are:

- Medical records (from any doctor, hospital or other healthcare provider)
- Information created or collected during the research. This could include your medical history, and dates or results from any physical exams, laboratory tests or other tests.

Who will receive information about you?
The study doctor and study staff will share your personal health information with:

- the sponsor, including persons or companies working for or with the sponsor
- Independent / Institutional Review Board
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- other regulatory agencies

Why will this information be used and/or given to others?
The sponsor and the groups above will use your health information:

- to complete this research
- to evaluate the results of the study
- to check that the study is being done properly
- to obtain marketing approval for new products resulting from this research

Is my health information protected after it has been given to others?
Your health information may be further shared by the groups above. If shared by them, the information will no longer be covered by this Authorization. These groups are committed to keeping your health information confidential.

What if I decide not to allow the use of my health information?
You do not have to sign this form. If you do not sign this form, you cannot take part in this research study.

May I withdraw or revoke (cancel) my permission?
YES. You may withdraw your permission to use and disclose your health information at any time. You can do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in the research study.

What happens if I want to withdraw my authorization?
Information that has already been gathered may still be used and given to others. If you withdraw your permission, no new health information will be gathered unless you have a side effect related to the study.

If you withdraw from the study but do not withdraw your Authorization, new health information may be collected until this study ends.

Will my authorization expire?
This Authorization will expire December 31, 2060, unless you withdraw it in writing before then.

May I review or copy the information obtained or created about me?
YES. You have the right to review and copy your health information. However, your access to this information may be delayed until the study is complete.

Your decision to withdraw your Authorization or not to participate will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

AUTHORIZATION
By signing this form, I allow the use or disclosure of my health information. I will receive a signed and dated copy of this Authorization.

Printed Name of Subject

Signature of Subject **Date**