Evaluation of anti-platelet factor 4/heparin antibodies in hemodialysis patients implanted with the GORE® Hybrid Vascular Graft versus non-heparin bonded synthetic vascular grafts.

Protocol Number: **HVG 13-01**

Amendment 2 06-Nov-2014

W. L. Gore & Associates, Inc.
Medical Products Division

Protocol Summary

Study Title	**Evaluation of anti-platelet factor 4/heparin antibodies in hemodialysis patients implanted with the GORE® Hybrid Vascular Graft versus non-heparin bonded synthetic vascular grafts.**
Protocol Number	HVG 13-01
Study Type	Post market clinical follow-up study (PMCF)
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 1505 N. Fourth Street Flagstaff, AZ 86004 Telephone: 800-437-8181
Study Design	Prospective, randomized, multi-center clinical study.
Study Objective	To characterize the GORE® Hybrid Vascular Graft as compared to non-heparin bonded synthetic vascular grafts in terms of the prevalence and persistence of anti-platelet factor 4/heparin antibodies (anti-PF4/H antibodies).
Study Hypothesis	The prevalence of *(i.e.,* percentage of patients with) anti-platelet factor 4/heparin antibodies will not be statistically different [redacted] in the GORE® Hybrid Vascular Graft test arm compared to the non-heparin bonded synthetic vascular graft study control arm at Day 7 and / or Day 14 as measured by a commercial poly-specific enzyme-immunoassay (EIA-GAM).
Study Endpoint and Additional Assessments	<u>Primary Endpoint:</u> • Prevalence of a positive commercial poly-specific enzyme immunoassay (EIA) at Day 7 and / or Day 14 time points [redacted]

	• [redacted]
Subject Population	End-Stage Renal Disease (ESRD) patients who have been on hemodialysis for [redacted] and require hemodialysis through an upper arm prosthetic vascular access graft.
Test Arm	GORE® Hybrid Vascular Graft
Control Arm	Non–heparin bonded synthetic graft
Number of Subjects	[redacted]
Number of Sites	Up to 25 sites in the U.S.
Expected Time to Complete Enrollment	18 - 24 months
Schedule of Events	• **Pre-procedure (within 2 days of Index Procedure)** – Collection of blood and serum samples, medical history, physical exam, review of inclusion and exclusion criteria, and proper consenting prior to any study procedure or data collection • **Index Procedure** - Implantation of vascular graft, [redacted], adverse events • **Day 7 (±2 days) -** Collection of blood and serum samples, adverse events, and revisions to the circuit • **Day 14 (±2 days)** – Collection of blood and serum samples, adverse events, and revisions to the circuit • **Day 30 (±7 days)** – Collection of blood and serum samples, [redacted], adverse events, and revisions to the circuit • **Day 90 (± 14 days)** – Collection of blood and serum samples, [redacted], adverse events, and revisions to the circuit • **Month 6 (± 14 days)** – Collection [redacted] adverse events, and revisions to the circuit • **Month 12 (± 14 days) –** Collection of [redacted], adverse events, and revisions to the circuit
Central Laboratory	[redacted]
Core Laboratory	[redacted]
Contract Research Organization	[redacted]

List of Abbreviations

aCRF	Annotated Case Report Form
ACT	Activated Clotting Time
AE	Adverse Event
AT	Antithrombin
AV	Arteriovenous
CA	Competent Authority
[redacted]	[redacted]
CBC	Complete Blood Count
CDMS	Clinical Data Management System
CDU	Color Flow Duplex Ultrasound
CFD	Computational Fluid Dynamics
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
cm	Centimeters
CM	Contrast Medium
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTA	Computed Tomographic Angiography
CVC	Central Venous Catheter
DIC	Disseminated Intravascular Coagulation
DIPA	Drug-Induced Platelet Activation Test
eCRF	Electronic Case Report Form
EIA	Enzyme Immunoassay
ePTFE	Expanded Polytetrafluoroethylene
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration (United States)
Fr	French (sizing)
GCP	Good Clinical Practice
GHVG	GORE® Hybrid Vascular Graft
[redacted]	[redacted]
Hb	Hemoglobin
HCT	Hematocrit
HIPA	Heparin-Induced Platelet Activation Test
HIT	Heparin-Induced Thrombocytopenia
ICF	Informed Consent Form

ICH	International Conference on Harmonisation
IFU	Instructions for Use
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRB	Institutional Review Board (U.S.)
ITT	Intent-to-Treat
LMWH	Low Molecular Weight Heparin
mm	Millimeters
NRS	Nitinol Reinforced Section
OD	Optical Density
PF4/H	Platelet Factor 4/heparin
PMCF	Post Market Clinical Follow-up
PTA	Percutaneous Transluminal Angioplasty
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Event
SRA	Serotonin Release Assay
UFH	Unfractionated Heparin

1. Introduction

In the United States more than 594,000 people are being treated for End Stage Renal Disease (ESRD).[1] Of this group, over 415,000 are on dialysis (either hemodialysis or peritoneal dialysis). ESRD is a growing health problem worldwide and is a strain on Medicare and other government health care programs. Since 2000, ESRD has increased by 23% in the US alone.[1] Medicare spends over $87,561 per patient annually for hemodialysis patients and over 33 billion dollars on ESRD patients in the US each year.[1]

Significant efforts have been made to increase the use of autogenous arteriovenous fistulas, however, the use of synthetic grafts still remains significant at 19.4% prevalence in 2012.[2] Expanded polytetrafluoroethylene (ePTFE) vascular grafts have been marketed in Europe and the United States for over 30 years. Since 1980, ePTFE has been the material of choice for small and medium diameter vascular grafts. The strong market presence and the extensive clinical history associated with ePTFE vascular grafts speak to the benefits of using these grafts for hemodialysis access. Distinct advantages of synthetic AV grafts include: large surface area available for cannulation, technically easy to cannulate, multiple insertion sites, variety of shapes and configurations, easy to handle, implant, and suture, and thrombosed grafts have longer patency rates after revision than do revised fistulas.[3]

Graft thrombosis accounts for approximately 80% of graft failures.[4] The clot is formed initially of platelet aggregates, and then fibrin and thrombin are laid down via activation of the coagulation cascade. One potential strategy to reduce this thrombogenicity is to covalently bind heparin to the luminal surface of the graft, imparting thromboresistant properties to the blood contact surface of the vascular graft. Heparin is a polysaccharide anticoagulant with a long history of clinical use in the prevention and treatment of thrombosis.

[redacted] The GORE® Hybrid Vascular Graft (incorporates this covalent, end-point immobilized heparin onto the luminal microstructure of the graft [redacted]

The complications with the use of non-heparinized vascular grafts are similar to the complications associated with vascular grafts with the [redacted][5] These complications include: fluid leakage, intraoperative bleeding, thrombosis, non-anastomotic and anastomotic circumferential tears, infection, seroma, pseudoaneurysm, and hematomas, etc. The low frequency of these complications relative to the large number of devices that have been implanted demonstrate the benefit of ePTFE grafts [redacted].[5]

Heparin-Induced Thrombocytopenia (HIT) is a potentially life threatening adverse reaction to heparin. Two forms of HIT have been described, HIT type I and HIT type II. The latter, HIT type II, is an immune-mediated reaction and is the more commonly discussed and more clinically significant version of HIT. The focus of this study is HIT type II and will hereafter be referred to simply as HIT. HIT is caused by heparin-dependent platelet-activating IgG antibodies that are formed in relation to an immunizing exposure to heparin, either unfractionated heparin (UFH) or low molecular weight heparin (LMWH). These antibodies recognize complexes of platelet factor 4 bound to heparin (PF4/H).[6] In a subset of these patients, these antibodies activate. These antibodies are clinically significant causing activation and aggregation of platelets resulting in a falling platelet count. In some patients this can lead to thrombotic complications. Among patients receiving systemic heparin, the reported incidence of HIT is between 0.1% to 5.0% depending on the patient population and heparin type. HIT occurs more frequently in surgical patients and with unfractionated heparin (UFH) than with low molecular weight heparin (LMWH). Patients sensitive to heparin may frequently develop HIT antibodies, however, thrombocytopenia and thrombosis are relatively uncommon consequences.[6]

The GORE® Hybrid Vascular Graft is contraindicated for use in patients with known hypersensitivity to heparin including those patients who have had a known incident if HIT. [redacted]

The risk of HIT for patients receiving systemic anticoagulant doses of heparin is low. Patients who receive the GORE® Hybrid Vascular Graft (GHVG) typically also receive systemic heparin both peri- and post-operatively and are therefore exposed to this low risk, independent of the implantation of a vascular graft [redacted]. An analysis of the [redacted] and [redacted] suggests that there is minimal risk that the covalently bonded heparin in the [redacted] causes or contributes to the condition of HIT.[5]

[redacted]

The clinical features of HIT include thrombocytopenia that bears a temporal relationship to the preceding immunizing exposure to heparin, thrombosis (venous or arterial), disseminated intravascular coagulation (DIC), post-UFH bolus anaphylactic reactions, limb gangrene, necrotizing skin lesions at heparin injection sites, among others.[7]

The key pathologic criterion for HIT is the presence of "HIT antibodies" as assessed by an in vitro SRA. The presence of HIT antibodies can be objectively determined with the SRA in concert with two enzyme immunoassays (EIAs), an IgG-specific EIA and a poly-specific EIA that detects antibodies of the Immunoglobulin G (IgG), Immunoglobulin A (IgA), and / or Immunoglobulin M (IgM) classes. A positive SRA has been shown to correlate strongly with the development of thrombocytopenia.[8] An unusual feature of "HIT antibodies" is their remarkable transience: typically, among patients with well-documented HIT, antibodies become undetectable after 50 to 85 days (depending on the assay performed).[9]

Patients who receive the GORE® Hybrid Vascular Graft, or any other synthetic vascular graft, are typically given systemic heparin peri-operatively or post-operatively and / or in the dialysis unit during hemodialysis sessions. Therefore, these patients are exposed to the established low risk of HIT, independent of the [redacted]

1.1. Study Rationale

The GORE® Hybrid Vascular Graft has been cleared by the U.S. Food and Drug Administration (FDA) in March 2010 for use in dialysis access patients, patients who require replacement or bypass of diseased vessels, trauma patients who need a vascular graft, and other vascular procedures.

Gore then submitted an application for CE-mark approval for the GORE® Hybrid Vascular Graft in 2012. The CE-mark was granted July 2012.

[redacted]

[redacted] Gore will conduct a controlled clinical study. Gore believes that a randomized, two-arm study to evaluate the prevalence and persistence of anti-PF4/heparin antibodies in GORE® Hybrid Vascular Graft patients versus a control arm (non-heparin bonded synthetic grafts) is the appropriate approach. By performing this type of controlled serology study, results of the study could potentially demonstrate there is no added risk of developing HIT antibodies through the use of a device [redacted]. In addition, the study could demonstrate that a device [redacted] does not influence the persistence of anti-PF4/H antibodies.

<u>Background of HIT in Hemodialysis Patients:</u>

The GORE® Hybrid Vascular Graft is used primarily for ESRD patients requiring hemodialysis through a synthetic graft. This study is to demonstrate that there is no added risk of developing HIT antibodies through the use of a device [redacted] (specifically the GHVG). The study will be conducted on a hemodialysis patient population in need of an upper arm synthetic arteriovenous (AV) access graft.

[redacted]

[redacted]

Background on HIT Assays:

Two general types of laboratory assays are used to confirm the presence of heparin-dependent IgG antibodies ("HIT" antibodies). Activation assays, such as the SRA, detect the antibodies based on their ability to activate platelets in a heparin-dependent fashion. Antigen assays, such as EIAs, detect the binding of antibodies to immobilized platelet factor 4-heparin complexes. The EIAs can be poly-specific (recognizing IgG, IgA and IgM immunoglobulin classes) or specific to detecting the IgG class alone. The antibodies associated with clinical HIT have been reported to be of the IgG class alone.

All three types of assays (SRA and both EIAs) will be performed on each serum sample at each time point by the [redacted]. All laboratory assays will be performed by [redacted] study personnel. The study personnel will be blinded to the clinical information including the type of graft implanted and any relevant clinical information, such as platelet counts.

1.2. Study Device Description

The GORE® Hybrid Vascular Graft is an ePTFE vascular prosthesis that has a section reinforced with nitinol (Figures 1, 2, and 3). The nitinol reinforced section (NRS) is partially constrained to allow for easy insertion and deployment into a vessel. The constraint is made up of an ePTFE fiber which is knitted into a tubular shape. The deployment line can be pulled to unzip the constraint and the NRS opens to its nominal diameter. The GORE® Hybrid Vascular Graft has a continuous lumen and includes the [redacted].

1.2.1. Vascular Graft Section

The GORE® Hybrid Vascular Graft is a single device that combines ePTFE and nitinol technologies. The device is constructed using an ePTFE base tube that extends the entire length of the device. The vascular graft section is comprised of ePTFE tubing, ePTFE reinforcing film, and ePTFE / FEP membrane, and includes an orientation line for ease of use during implantation. The microstructure of ePTFE consists of nodes and fibrils and is porous throughout.

Figure 1. Schematic drawing of the nitinol reinforced section of the GHVG showing the constrained NRS with the deployment line (top) and the fully deployed NRS (bottom).

Figure 2. The GORE® Hybrid Vascular Graft with the constrained nitinol reinforced section.

Figure 3. The GORE® Hybrid Vascular Graft fully deployed.

1.2.2. Nitinol Reinforced Section

The nitinol reinforced section (NRS) is comprised of ePTFE tubing, ePTFE reinforcing film, ePTFE / FEP membrane, nitinol, and an ePTFE / FEP film that bonds the nitinol section to the ePTFE reinforcing film. The NRS has a reducible diameter for loading into the constraint / delivery system and has sufficient radial force to resist migration when deployed into a blood vessel with proper over sizing.

1.2.3. Constraint / Delivery System The constraint / delivery system is comprised of an ePTFE fiber which is knitted into a tubular shape. A portion of the nitinol reinforced section is loaded into the constraint / delivery system such that the loaded section can be inserted into a blood vessel.

[redacted]

[redacted]

[redacted]

1.2.5. Configurations

Below is a table of the current configurations of the GORE® Hybrid Vascular Graft.

Catalog Number (U.S.)	Nitinol Reinforced Section	Vascular Graft Section
0650HYB0605A	6 mm x 5 cm	6 mm x 50 cm
0650HYB0610A	6 mm x 10 cm	6 mm x 50 cm
0650HYB0705A	7 mm x 5 cm	6 mm x 50 cm
0650HYB0710A	7 mm x 10 cm	6 mm x 50 cm
0650HYB0805A	8 mm x 5 cm	6 mm x 50 cm
0650HYB0810A	8 mm x 10 cm	6 mm x 50 cm
0650HYB0905A	9 mm x 5 cm	6 mm x 50 cm
0650HYB0910A	9 mm x 10 cm	6 mm x 50 cm

1.2.6. Indications for Use

GORE® Hybrid Vascular Grafts are intended for use as vascular prostheses for replacement or bypass of diseased vessels in patients suffering occlusive or aneurysmal diseases, in trauma patients requiring vascular replacement, for dialysis access, or for other vascular procedures.

1.2.7. Contraindications

DO NOT use the GORE® Hybrid Vascular Graft in patients with known hypersensitivity to heparin, including those patients who have had a previous incident of HIT type II. DO NOT use any configuration of GORE® Hybrid Vascular Grafts for coronary artery bypass or cerebral reconstruction procedures. DO NOT use GORE® Hybrid Vascular Grafts as a patch. If cut and used as a patch, GORE® Hybrid Vascular Grafts may lack adequate transverse strength. Refer to *Instructions for Use* at goremedical.com for a complete description of all warnings, precautions and adverse events.

1.2.8. Implantation

The GORE® Hybrid Vascular Graft includes the nitinol reinforced section which facilitates the fast and simple creation of an end-to-end anastomosis. There are two basic implantation techniques for placing the GHVG: a standard open surgical technique and an over-the-wire technique.

1.2.9. Unique Benefits and Features

[redacted]

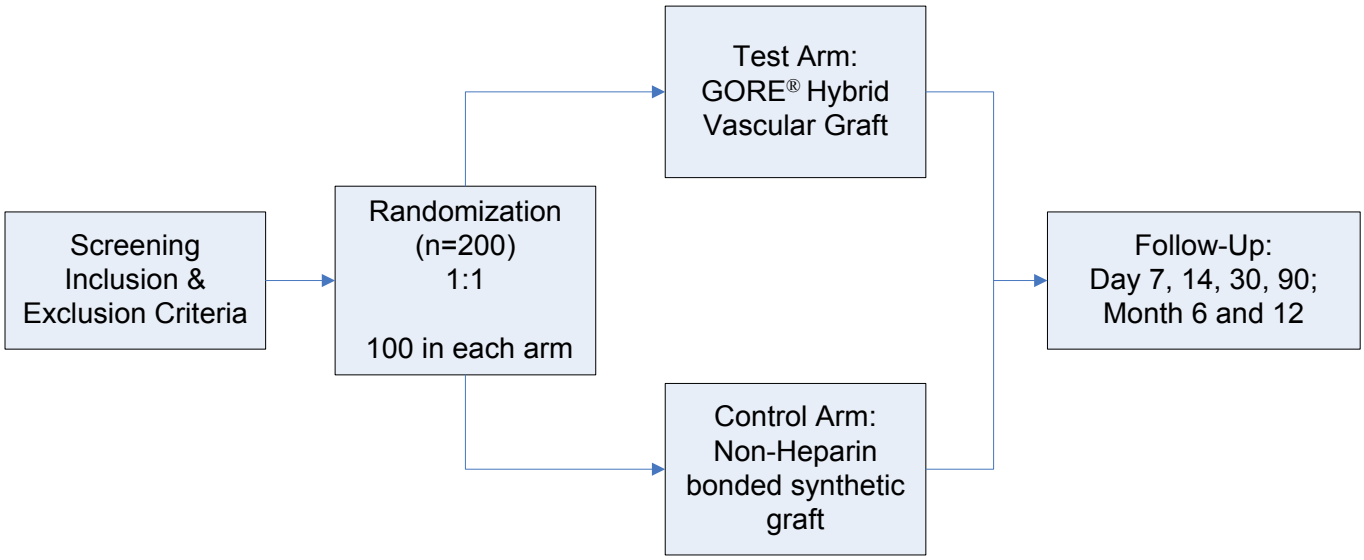
2. Study Objective

To characterize the GORE® Hybrid Vascular Graft as compared to non-heparin bonded synthetic vascular grafts in terms of the prevalence and persistence of anti-platelet factor 4/heparin antibodies (anti-PF4/H antibodies) up to Day 90.

[redacted]

3. Study Design

3.1. Study Design Schema



3.2. Description of Study Design

This is a prospective, multicenter, randomized clinical evaluation to characterize the GORE® Hybrid Vascular Graft by comparing non-heparin bonded synthetic vascular grafts in terms of the prevalence and persistence of anti-PF4/H antibodies up to Day 90.

[redacted]

Subjects may continue into the extended portion of this clinical study (post Day 90) provided the vascular graft has not been abandoned. Subjects will return for follow-up visits at Months 6 and 12. The control device is a non-heparin bonded synthetic vascular graft that is indicated for use for dialysis access. The control graft may be composed of any synthetic material including, but not limited to: [redacted] The brand of the control device is at the discretion of the Investigator. [redacted]

A maximum of 25 Clinical Investigative Sites (referred to as "Sites" in the remainder of this document) in the United States will participate in this study [redacted]

Follow-up Schedule

- **Day 7 (±2 days) -** Collection of blood and serum samples, adverse events, and revisions to the circuit
- **Day 14 (±2 days)** – Collection of blood and serum samples, adverse events, and revisions to the circuit
- **Day 30 (±7 days)** – Collection of blood and serum samples, [redacted], adverse events, and revisions to the circuit
- **Day 90 (± 14 days)** – Collection of blood and serum samples, [redacted], adverse events, and revisions to the circuit
- **Month 6 (± 14 days)** - [redacted], adverse events, and revisions to the circuit
- **Month 12 (± 14 days)** - [redacted], adverse events, and revisions to the circuit

Patients may be enrolled into the clinical study provided all inclusion and no exclusion criteria are met as specified in Section 4. Subjects will be evaluated through surgical discharge and return for follow-up visits at Days 7, 14, 30, 90, Months 6 and 12.

3.3. Study Endpoint and Additional Assessments

3.3.1. Primary Endpoint

Prevalence of a positive poly-specific enzyme immunoassay (EIA) at Day 7 and / or Day 14 time points (Appendix B)

The primary endpoint will have been satisfied when subjects complete Day 90.

3.3.2 [redacted]

[redacted]

4. Study Population

4.1. Description of Population

Patients with End-Stage Renal Disease are eligible for screening for participation in the study. The Site may screen patients that are currently receiving hemodialysis through a central venous catheter (CVC), graft, or fistula and are expected to require hemodialysis through an upper arm prosthetic vascular graft.

The study has been designed with standard eligibility criteria to address any known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results. Only patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled.

4.2. Inclusion Criteria (all responses must be YES to be eligible)

1. The patient is not a candidate for a native fistula.
2. The patient requires the creation of an upper arm vascular access graft for hemodialysis secondary to a diagnosis of End-Stage Renal Disease.

[redacted]

4.3. Exclusion Criteria (all responses must be NO to be eligible)

1. The patient is scheduled for a different surgical procedure within 30 days post Index Procedure.

[redacted]

3. The patient has a known hypercoagulable disorder or bleeding disorder.

4. The patient has had a previous instance of Heparin Induced Thrombocytopenia Type II (HIT type II) or has known sensitivity to heparin.

[redacted]

5. Study Procedures / Evaluations

Demographic information such as age, gender, ethnicity, and race will be recorded as well as medical history including, but not limited to, diabetes, hypertension, coronary artery disease, peripheral arterial disease, tobacco use, and other co-morbid conditions. Height and weight will also be collected pre-procedure. Acknowledging the fact the weight of hemodialysis patients can vary greatly between treatments, the weight listed in the medical chart at the time of screening visit will be considered the pre-procedure weight.

The Investigator will also collect a vascular access history which will include the following: date the Subject originally started hemodialysis, whether a fistula, graft, or CVC is currently being used for hemodialysis, and number of previous vascular accesses.

It is expected that the Subject will follow the standard institutional patient care protocol at the discretion of the Investigator in regards to venous mapping, lab work, etc., prior to study procedure.

5.1 Laboratory Specimens

This clinical study is evaluating anti-PF4/H antibodies at five time points [redacted] Sites are required to draw blood and collect serum samples at the specified follow-up intervals. Site personnel should have appropriate credentials / certifications to draw blood and collect serum per local regulations or send Subjects to an appropriate facility to have blood samples drawn.

Each Site will be responsible for shipping the blood and serum samples to the central laboratory [redacted] Prior to shipping, the Site will pack and ship the samples per laboratory manual instructions.

The Gore Clinical Study Manager will ensure the Site has an adequate amount of specimen kits and shipping materials.

5.2 Schedule of Events

	Pre-Operative	Procedure	Post Op Day: 7	Post Op Day: 14	Post Op Day: 30	Post Op Day: 90	Post Op Month: 6	Post Op Month: 12
Informed Consent	X							
Inclusion/Exclusion Criteria	X							
Demographics & Medical History	X							
Vascular Access History	X							
Physical Exam	X		X	X	X	X	X	X
Blood Draw	X		X	X	X	X		
Device Placement		X						
Palpable Thrill and / or Bruit		X	X	X	X	X	X	X
[redacted]		X			X	X	X	X
Revisions to Circuit			X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X

5.3 Informed Consent Process

All patients must provide informed consent prior to any study-related procedures being performed. The case history (*i.e.,* source documents / Subject chart) for each Subject shall document such informed consent was obtained. The Institutional Review Board (IRB) approved consent form (ICF) will be signed and personally dated by the Subject or his / her legally authorized representative, and the Investigator / designee who conducted the informed consent discussion.

Subjects enrolled under the original protocol (3-DEC-2013) should not be re-consented under Amendment 2[redacted] if:

- the vascular graft has been abandoned prior to the Day 90 follow-up visit
- the vascular graft has been explanted

[redacted]

[redacted]

The original signed ICF(s) will be retained in the Subject records. A copy of the signed informed consent document will be given to the Subject for their records.

5.4 Screening

All patients who sign an informed consent form will be considered entered into the screening phase of the study. Subjects who sign an ICF are not assigned a subject ID until randomization.

The Site will keep signed informed consent forms on all screen failures and keep a record of the reason the Subject failed screening. Site will also keep any laboratory reports for those samples that were sent to [redacted] for processing.

If the Subject withdraws from the study prior to randomization, pre-procedure blood / serum samples need to be destroyed by either [redacted] or the Site. If the Site has the pre-procedure blood / serum samples, then the Site should destroy them per their institutional standards. If the pre-procedure blood / serum samples have already been shipped to [redacted], then [redacted] will be notified by Site and / or Sponsor to destroy the samples.

Case report forms (CRF) will not need to be completed for Subjects who are withdrawn from the study prior to randomization.

5.5 Enrollment

The patient is considered to be formally enrolled in the study when the randomization envelope, with the correct Subject ID number sequence, is opened before or during the Index Procedure.

If the Subject has been randomized (randomization envelope opened) and is unable to complete the index procedure, then the Subject will be discontinued from the study. CRFs will still be completed to reflect screening activities, procedure, and discontinuation. Pre-procedure blood and serum samples should be shipped to Covance for processing.

5.6 Procedure

Routine surgical practice for implantation of the vascular graft as an upper arm arteriovenous access for hemodialysis per the Investigator's standard of practice should be used. The test device, GORE® Hybrid Vascular Graft, is available in eight configurations listed in Section 1.2.5. The GHVG will be provided at standard cost.

5.6.1 Test Device Training Requirements

If the study Site has not used the GHVG, the study Site must complete device training prior to Subject enrollment.

5.6.2 Implantation Technique

The Investigator is expected to follow the Instructions for Use (IFU) for the test device or the control device, as determined by randomization.

5.6.3 Additional Implant Considerations

When implanting the GORE® Hybrid Vascular Graft or control device, the following considerations are recommended:

- The correct graft length for each procedure should be carefully determined according to the Investigator's standard practice.
- Any unused portions of the vascular graft must be destroyed according to institutional standards.
- Create a tight subcutaneous tissue tunnel.
- Avoid the use of traumatic clamps on vessels or vascular graft.
- If possible, avoid the use of systemic heparin during the index procedure.

The study procedure is considered to be a success once a thrill and / or bruit is noted through the implanted vascular access graft. The total procedural time, defined as the time from the first incision to the completion of closing of the last incision, will be recorded on the Procedure CRF.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.7 Follow-Up

There are six (6) scheduled follow-up visits in this study. Follow-up visits are at following intervals:

- Day 7 (±2 days)
- Day 14 (±2 days)
- Day 30 (±7 days)
- Day 90 (±14 days)
- Month 6 (±14 days)
- Month 12 (±14 days)

Follow-up visits will be scheduled at appointed times after the date of treatment (Index Procedure). [redacted] The Sponsor recognizes that Subjects may not be able to return for follow-up visits on the exact day required, therefore a plus / minus window has been allotted for each visit.

[redacted]

[redacted]

Refer to the Schedule of Events (Section 5.2) for follow-up visit requirements.

5.8 Revisions to the Vascular Access Circuit

Subjects may need revisions to the vascular access circuit (either test / control arm). An appropriate clinical indication (*e.g.,* stenosis, thrombosis, low blood flow, elevated venous pressures, etc.) must be present to trigger a revision to the vascular access circuit.

It is recommended that, when possible, Subjects return to the Investigator for revisions; however, it is understood Subjects may be unable to return to the Investigator for revision procedures. If a revision is not performed by the Investigator, attempts should be made to collect revision data from the facility that performed the procedure. This information can be communicated to the Site via fax, electronic communication, and / or documented phone communication, etc.

5.9 Subject Withdrawal from the Study

The Subject may voluntarily withdraw from the study at any time and should notify the Investigator in this event. The Investigator may also withdraw the Subject from the clinical study at any time based on his / her medical judgment. A Study Completion / Discontinuation CRF should be completed for these Subjects.

5.10 Subject Lost to Follow-Up

The Site will record their documented attempts to schedule follow-up visits with the Subject.

The Subject will be considered lost to follow-up at the end of the study if the Subject does not complete the Month 12 follow up visit. If the Subject is considered lost to follow-up, the last follow-up visit date will be considered their date of discontinuation.

5.11 Subject Study Completion and Discontinuation

A Study Completion / Discontinuation CRF will be completed for each enrolled Subject at the conclusion of his / her participation in the study. The reason for completion or discontinuation for each Subject should be documented (*e.g.*, Subject completed the study per protocol requirements, expired, vascular graft explanted, or lost to follow-up).

If the Subject expired, the date of death will be recorded. The Investigator will assess whether the death was related to the vascular device, if applicable.

5.12 Device Deficiencies

The vascular grafts used in the test arm (GORE® Hybrid Vascular Graft) and control arm are not investigational. Any GORE® Hybrid Vascular Graft deficiencies will be reported through normal product surveillance procedures.

5.13 Explant Procedures

The GORE® Hybrid Vascular Graft may be explanted during a surgical procedure or as part of an autopsy. Sites are requested to return explanted device(s) to the Sponsor for gross and histological evaluation. Prior to planned or potential device retrieval, contact the Gore Associate managing the study to communicate that a specimen is being retrieved from a study Subject. A specimen shipping kit will be immediately sent to the Site. The specimen kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

6. Clinical Study Administration

6.1 Training

Sites selected for this clinical study must be approved to use the GORE® Hybrid Vascular Graft.

6.2 Monitoring

Site monitoring for this study will be provided by [redacted]. Monitoring oversight will be provided by the Sponsor.

The Site monitors are qualified by training and experience to oversee the progress of the study at the Site and will ensure that the Investigators and their staff understand and adhere to both the applicable regulatory requirements and the study protocol. In addition, they may assist in resolution of any problems that may arise during the study.

Site Initiation

Site initiation will be performed to assure that each Investigator and his / her staff understands the protocol, applicable regulations, human subject protection requirements, and the Investigator's obligations. This visit will ensure that required training documentation with the appropriate IRB approvals are in place prior to Subject enrollment.

Periodic Site Monitoring

Periodic Site monitoring will occur as necessary to ensure continuing adequacy of facilities and adherence to the clinical study protocol, GCPs, and applicable regulations and laws that pertain to the conduct of the clinical study. These activities will also include the review of CRFs, source documentation, resolution of any missing or inconsistent data, timely submission of accurate records to the Sponsor, and the maintenance of proper records. A report will be written following each Site visit and a follow-up letter will be provided to the Site with a summary of findings. Each Site will also be visited at close-out to ensure all documentation is complete.

6.3 Device Accountability and Storage

The GORE® Hybrid Vascular Graft is a commercially available device and does not require device accountability tracking. As part of procedure data collection, the Investigator will record device lot numbers and catalog numbers on the CRF.

6.4 Central Laboratory

Central laboratory services for this study will be provided by [redacted]. [redacted] will provide Sites with kits for collecting and shipping blood and serum samples through Day 90. [redacted] will also perform a hematology panel with differential and provide results to the Sites.

[redacted]

[redacted]

6.5 Core Laboratory

Core laboratory services for this study will be provided by [redacted] through Day 90. The core laboratory will analyze serum for anti-platelet factor 4/heparin antibodies by EIA-GAM, [redacted].

6.6 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control. The Principal Investigator is responsible for promptly reporting protocol deviations to his or her IRB per IRB policy and the Sponsor. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and Subject safety and determine if additional reports or actions are required. Additional action may include Site retraining and / or Site termination from participation in the trial.

The Investigator will not implement any changes to the protocol without first obtaining written agreement from the Sponsor and documented approval from the IRB except in the event of an immediate hazard(s) to a Subject. The Investigator will report the deviation in accordance with the applicable regulations.

6.7 Clinical Data Review

Clinical data will be reviewed at periodic intervals to ensure consistent and accurate reporting. Cases to be reviewed will include, but will not be limited to, adverse events, protocol deviations, and study procedures. Data will be reviewed by the Clinical Study Team and will include the Sponsor's Product Specialist and at least one medical director.

6.8 Protocol Amendments

The Investigator will obtain IRB approval on all amendments in a timely manner. The Sponsor will ensure proper training of Investigator and Site staff on all protocol amendments.

6.9 Sponsor Representatives

Sponsor field representatives / clinical staff may be present during study procedures to provide technical assistance to the Investigator in the use of the device. The activities of these Sponsor representatives will be supervised by the Investigator to avoid bias, ensure data quality, and protect patient rights.

6.10 Access to Source Data / Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the clinical investigation.

The Investigator will keep all study records and source data for inspection by the Sponsor, Sponsor's monitors, IRB, and regulatory authorities.

6.11 Study Records Retention

The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Clinical study records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but not be limited to:

- All correspondence with another investigator, an IRB, the Sponsor, a monitor, a regulatory body, including required reports.
- Records of each Subject's case history and exposure to the device. The case history for each Subject shall document that informed consent was obtained prior to participation in the study. Case histories include the following:
    - Case report forms
    - Signed and dated consent forms and documents evidencing informed consent
    - Medical records (*e.g.,* progress notes of the physician, the Subject's hospital chart(s), and the nurses' notes
    - For any use of a device without informed consent, a written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain the informed consent.
    - All relevant observations, including records and date and condition of each Subject upon entering, and information about relevant previous medical history and the results of all diagnostic tests.
- The protocol, any amendments, and documentation of any deviations from the protocol, including the dates and the reasons for such deviations.
- A certification stating the IRB is in compliance with FDA regulations.
- Any other records as required by the IRB and the Sponsor.

The Investigator will prepare and submit the following reports:

- Withdrawal of IRB approval: The Investigator will report any withdrawal of approval within five working days after the Investigator has been notified of the withdrawal.
- Progress reports: Progress reports documenting the procedure, AEs, and follow-up data concerning individual Subjects will be submitted to the Sponsor on standardized CRFs. The Investigator may also be required to submit progress reports and final reports to the IRB and to the Sponsor summarizing the Investigator's experience during the study.
- Protocol Deviations shall be reported as described in Section 6.6.
- Other: Any other reports as reasonably requested by the Sponsor or required by applicable local regulations.

6.12 Clinical Trial Registration

If applicable, the Sponsor will register the study and post results as required by applicable U.S. laws and regulations.

7. Data Collection and Submission

The Clinical Data Management System (CDMS) for this study will be provided by [redacted]

7.1 Data Collection Methods

This study will report clinical data using the software utilized by [redacted]. The CDMS will be the database of record for the protocol and subject to regulatory inspections. All users will be trained to use the CDMS and will comply with study-specific guidelines / instructions as well as applicable regulatory requirements.

Subject data will be collected using protocol-specific CRFs. Site staff and core laboratory will enter data directly into the CRF for transmission to the Sponsor. The Sites will be notified of any significant amendments to the CRFs.

7.2 Data Clarification and Correction

Once entered, data will be evaluated to ensure it is complete, consistent, and logically sound. If changes to the data in the CDMS are required, all changes, reasons for changes, and persons making the changes will be captured in the CDMS' audit trail.

8. Risk Assessment

8.1 Potential Risks

The risks associated with the GORE® Hybrid Vascular Graft for use in hemodialysis are expected to be similar to the risks associated with the use of non-heparin bonded synthetic vascular grafts.

Risks associated with these devices, including the GORE® Hybrid Vascular Graft, or the surgical procedure include but are not limited to:

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

In comparison to patients receiving standard vascular grafts for hemodialysis, the only additional potential risks to Subjects enrolled in this clinical study are the bioactive heparin on the luminal surface and the insertion of the NRS of the GHVG. All other aspects of the vascular graft are equivalent.

8.2 Minimization of Risks

Potential risks associated with the use of the GORE® Hybrid Vascular Graft may be minimized by the following activities:

- Testing: The Sponsor has performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production. Investigators will be selected who are knowledgeable and experienced in vascular graft implantation procedures.
- Training: Comprehensive Site Investigator and staff training will be conducted to share information regarding design and proper use of the GORE® Hybrid Vascular Graft.
- Training: The Site Investigator, Sub-Investigators, Study Coordinator(s) or designee at each Site will be trained to the protocol and Subject follow-up requirements.
- Screening: Protocol inclusion / exclusion criteria and follow-up schedule are designed to select appropriate Subjects and identify potential complications early. Subjects will be assessed post-procedure and subsequently on a regular basis at their follow-up visits.
- Monitoring: Data completed by the clinical Sites will be monitored to evaluate protocol compliance, accuracy, and Subject safety.
- Sharing: Data during the clinical study will be shared with the Site Investigators to aid understanding of the device and potential complications associated with its use.

9. Adverse Events

Adverse events (AEs) are defined as any untoward medical occurrences in a Subject whether device-related or not.

9.1 Anticipated Adverse Events

Anticipated adverse events are complications that are known to be associated with hemodialysis patients undergoing the creation of vascular graft access. See Section 8, Risk Assessment.

The Sponsor considers occurrences of thrombosis and stenosis to be efficacy outcomes and not adverse events. These occurrences should be reported on a Revision to Circuit CRF. Should there be clinical sequelae associated with thrombosis and stenosis, these sequelae are considered adverse events and should be reported.

9.2 Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device, procedure, or disease.

Study Device-related (Hybrid or Control Graft)

The functioning or characteristics of the device caused or contributed to the AE.

Study Procedure-related (Index Procedure)

The index procedure (and not the device) caused or significantly contributed to the AE.

Disease-related (ESRD only)

The AE was a result of the underlying disease progression, for which the study procedure is being performed, and not the device or procedure.

Not-related

An AE which cannot be attributed to the device, procedure, or disease.

Unknown relationship

The relationship of the AE to the device, procedure, or disease cannot be determined.

9.3 Adverse Event Classification

The Investigator at each Investigative Site is ultimately responsible for reporting AEs to the Sponsor. The Investigator is required to complete the appropriate CRFs to report the occurrence of AEs.

Each AE will be assessed by the Investigator to determine if it is a serious adverse event (SAE).

A Serious Adverse Event (ISO 14155 definition) is an Adverse Event that

- led to death
- led to serious deterioration in the health of the Subject that either resulted in
  - a life threatening illness or injury, or
  - a permanent impairment of a body structure or body function, or
  - inpatient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
- led to fetal distress, fetal death, or a congenital abnormality or birth defect.

Emergency room visits and 23-hours observations are not considered hospitalizations.

9.4 Adverse Event Reporting and Coding

AEs will be reported on the appropriate case report form and documented in the Subject's permanent medical record.

The following information on each reported adverse event will be collected:

- Adverse Event Term
- Adverse Event Onset Date
- Relationship
- Severity
- Treatment
- Outcome
- Resolution Date

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

AE submission guidelines:

- AE reporting begins once the patient is enrolled in the study. All AEs should be reported from enrollment (study procedure) through study completion / discontinuation.
- Provide a diagnosis if possible. If unable to provide a diagnosis, report the symptoms as separate events. AEs should be reported using the full name without abbreviations or narratives.
- AEs with an outcome status of "Ongoing" should be assessed at each follow-up evaluation to determine if the event has resolved. AEs ongoing at study completion / discontinuation should be completed as "Ongoing" on the AE CRF.

9.5 Subject Death

When a Subject in the study expires, the primary cause of death will be identified as the AE. If any AEs have been reported as "Ongoing" up through the time of a Subject's death, these events would then become resolved with the date of death.

An effort by the Site should be made to collect additional information regarding the Subject's death. Documents include, but are not limited to: autopsy reports, death certificates, lab reports, and other applicable medical records.

A Study Completion / Discontinuation CRF will be completed for each Subject who expired during the course of the study.

10. Statistical Analysis

10.1. Study Hypothesis

[redacted]

The hypothesis is specified as follows:

[redacted]

10.2. Sample Size Assumptions

[redacted]

10.3. Sample Size Determination

[redacted]

10.4. Randomization Scheme

The randomization will be organized using [redacted] Any irregularity in the randomization process will be documented and reported to the Sponsor.

10.5. Blinding Scheme

The Subjects, as well as treating physicians, will be aware of the type of implanted graft. However, the core laboratory responsible for analyzing the blood samples will be blinded to the actual type of graft.

10.6. Data Analysis

10.6.1. Timing of Analyses

[redacted]

[redacted]

10.6.2. Analysis Populations

10.6.2.1. Intent-To-Treat (ITT)

The intent-to-treat population is defined as all enrolled subjects analyzed by the assigned treatment arm at the time of randomization.

10.6.2.2. As Treated

The “as treated” population is defined as all subjects analyzed by type of the actual implanted device.

[redacted]

10.6.3. Pooling of Data

Data will be pooled from all Sites participating in the trial. To help ensure homogeneity of data across Sites, the protocol will be administered and monitored in a uniform manner at all Sites.

[redacted]

10.6.4. Statistical Analysis of Primary Endpoint(s)

[redacted]

11. Ethical and Regulatory Considerations

11.1. Statement of Compliance

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and applicable regulatory requirements.

The following are applicable to this study:

21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 50	Protection of Human Subjects
21 CFR Part 56	Institutional Review Boards
ICH-GCP E6	International Conference on Harmonisation Regulations Guideline For Good Clinical Practice

11.2. Compliance Responsibilities

The Sponsor will conduct the clinical study in accordance with all applicable regulations and laws. The Sponsor will be responsible for documenting that Investigators have the necessary skills, training, and information to properly conduct the clinical study. The Sponsor will ensure proper monitoring of the clinical study and ensure the Site has obtained IRB approval prior to enrollment. The Sponsor will provide information to the Investigators and the reviewing IRB concerning the progress of and any new material information about the clinical study.

The Investigator will conduct the clinical study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing IRB. The Investigator will ensure IRB approval is obtained prior to enrollment, maintained throughout the course of the study, and all IRB reporting requirements are met. The Investigator is responsible for protecting the rights, safety, and welfare of Subjects under the Investigator's care and for the control of devices under investigation. The Investigator is also responsible for ensuring informed consent is properly obtained.

11.3. Informed Consent

The Investigator shall ensure all potential Subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.

The formal consent of a Subject, using the IRB-approved consent form, must be obtained by the Investigator before that Subject undergoes any study-related procedure. The consent form will be signed and personally dated by the Subject or legally authorized representative, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the Subject records. A copy of the signed informed consent document will be given to the Subject for his or her records. Any significant, new information which emerges while the study is in progress that may influence a Subject's willingness to continue to take part in the study will be provided to the Subject.

The Investigator shall ensure documentation of the acquisition of informed consent is recorded in each Subject's records in accordance with applicable regulations.

11.4. Independent Ethical Review

The Investigator shall not enroll any Subjects prior to obtaining approval for the study from a properly constituted independent IRB.

The Investigator will submit the protocol, informed consent forms, other information to be provided to Subjects such as survey instruments or questionnaires, and any proposed advertising / recruitment materials to the IRB for written approval.

11.5. Conflict of Interest

All Investigators will follow their Institution's conflict of interest policies.

11.6. Confidentiality

All Subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

Such records may also be reviewed by the Site's IRB and other regulatory bodies.

The Investigator will inform the Subjects their records will be reviewed.

12. References

[redacted]