A randomized controlled comparative study on efficacy and cost-effectiveness of heparin-bonded versus non-heparin-bonded polytetrafluroethylene hemodialysis access grafts.

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Study Protocol Title

Full Title:

A randomized controlled comparative study on efficacy and cost-effectiveness of heparin-bonded versus non-heparin-bonded polytetrafluroethylene hemodialysis access grafts.

Alias/Short Title:

PRICE - Propaten Randomized Investigation on Cost-benefit and Efficacy

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List of Abbreviations:

PTFE – polytetrafluroethylene

AVG – Arteriovenous graft

AE - Adverse Event/Adverse Experience

CFR - Code of Federal Regulations

CIB - Clinical Investigator's Brochure

CIOMS - Council for International Organizations of Medical Sciences

CONSORT - Consolidated Standards of Reporting Trials

CRF - Case Report Form

CRO - Contract Research Organization

DCC - Data Coordinating Center

DSMB - Data and Safety Monitoring Board

DSMC - Data and Safety Monitoring Committee

FDA - Food and Drug Administration

FWA - Federal-Wide Assurance

GCP - Good Clinical Practice

HIPAA - Health Insurance Portability and Accountability Act

IB - Investigator's Brochure

ICAVL – Intersocietal Commission Accreditation for Vascular Laboratories

ICF - Informed Consent Form

ICH - International Conference on Harmonization

IDE - Investigational Device Exemption

IEC - Independent or Institutional Ethics Committee

IND - Investigational New Drug IRB

- Institutional Review Board ISM -

Independent Safety Monitor

MedDRA © - Medical Dictionary for Regulatory Activities

MOP - Manual of Procedures

N - Number (typically refers to participants)

NCI - National Cancer Institute, NIH

NDA - New Drug Application

NIAID - National Institute of Allergy and Infectious Diseases, NIH

NIH - National Institutes of Health

OHRP - Office for Human Research Protections

OHSR - Office for Human Subjects Research

PHI - Protected Health Information

PI - Principal Investigator

PK - Pharmacokinetics

QA - Quality Assurance

QC - Quality Control

RVT – Registered Vascular Technologists

SAE - Serious Adverse Event/Serious Adverse Experience

SMC - Safety Monitoring Committee

SOP - Standard Operating Procedure

WHO - World Health Organization

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Research Synopsis

Study Title

A randomized controlled comparative study on efficacy and cost-effectiveness of heparin-bonded versus non-heparin-bonded polytetrafluroethylene hemodialysis access grafts.

Clinical Phase

Phase IV clinical Trial

Study Population

The study will target all adult patients aged 18 years and above who present or are referred to the institution with a need for an arteriovenous vascular access for hemodialysis over a period of 5 years.

Study Design

A multicenter, single-blinded, randomized controlled trial.

Sample Size

200 total enrollment with possible screen failures.

Study Duration

The study will accrue patients over the course of 5 years.

Study Agent and Intervention Description

Heparin-bonded polytetrafluoroethylene grafts (GORE PROPATEN® or ACUSEAL® Vascular Graft) vs. conventional expanded polytetrafluoroethylene grafts (GORE-TEX® Stretch Vascular Graft).

Primary Objective

- *To assess the efficacy of Propaten (or ACUSEAL®) versus standard ePTFE vascular grafts*

Primary Outcome Measures:

- *Primary, primary-assisted and secondary patency rates.*

Secondary Objectives

- *To evaluate and compare the overall morbidity, mortality and patient's quality of life.*
- *To compare and analyze the estimated costs with both types of interventions and their outcomes.*

Secondary Outcome Measures:

- *Complication or morbidity rates associated with both types of interventions.*
- *Number of postoperative reinterventions associated with both types of graft interventions.*
- *Cost estimation and analysis associated with both types of graft interventions.*
- *Quality of life as measured by the SF-12v2® Health Survey Standard.*

Background and Significance:

Several factors affect hemodialysis access patency but the choice of conduit remains a major determinant. The National Kidney Foundation Dialysis Outcomes Quality Improvement guidelines recommend native veins over prosthetic grafts for arteriovenous access conduits. Native vessel arteriovenous fistulae (AVF) have higher patency rates and lower complications than prosthetic arteriovenous grafts (AVGs).[1-4] Clinical exam and noninvasive imaging, such as ultrasound vein mapping, indicate suitability of native veins for arteriovenous fistulae. Physical attributes of the inflow and outflow vessels predispose successful arteriovenous access maturation including arterial diameter > 1.5 mm and venous diameter > 2.5 mm and an elevated intimal-medial thickness (IMT) has been shown to be predictive of AVF failure.[5-8]

When no suitable native veins are available, prosthetic graft is an accepted alternative. Expanded polytetrafluoroethylene (PTFE) is the most commonly used prosthetic conduit. Our recently published analysis showed a 1-year cumulative patency rate of 67% for standard AVG compared with 83% for AVF (p=0.0001). Given the worse outcomes with AVG, manufacturers have tried to improve patency by changing the shape of the grafts such as cuffed [9] and tapered ends. Recently, heparin anticoagulant has been covalently bonded to the inner lumen of the PTFE graft (PROPATEN®). The same manufacturers who designed this hemodialysis graft have recently launched a new graft (ACCUSEAL®) that in addition to being heparin-bonded also includes an elastomeric middle membrane between inner and outer layers of expanded polytetrafluoroethylene (ePTFE). This additional layer allows early cannulation within 24 hours after implantation and can prevent suture line and cannulation needle associated bleeding, risk of seroma, and pseudoaneurysm formation. Short-term results from a prospective, non-randomized, multi-center US clinical trial on this FDA-approved ACCUSEAL® vascular

graft,[10] demonstrate early cannulation was possible within 72 hours of the graft implantation and 75.6% were successfully cannulated at least three consecutive times within 28 days of graft implantation. This allowed for significant reduction in the number of days patients required tunnelled catheters for dialysis and in turn reduction in associated morbidity and mortality for these patients [10].

Besides the self-sealing and kink resistant technology of the new ACUSEAL® vascular graft, in all remaining aspects, such as graft handling and design flexibility, it is consistent with standard-wall as well as heparin-bonded (PROPATEN®) dialysis vascular grafts. Furthermore, the ePTFE luminal surface of this graft incorporates the same covalently bonded heparin technology (CBAS® Heparin Surface) anchored to the graft surface as the one used in the PROPATEN® graft. This heparin-bonded layer imparts proven thromboresistant properties to the vascular graft as well as sustained bioactivity that has been described before with the PROPATEN® graft. Since the introduction of this graft in 2013 and with the publication of results from the recent clinical trial, nationwide vascular surgeons increasingly prefer the use of new dialysis graft (ACCUSEAL®) over the previous generation (PROPATEN®).

No published randomized trials are available that show benefit with heparin-bonded AVGs. Shemesh et al have yet to publish final results from their randomized study which looked at forearm looped grafts as initial access in Israeli patients.[11] It is unclear if their results will be applicable to the broader U.S. population and in patients with prior failed access. Davidson et al showed a 20% improvement in patency with heparin-bonded grafts compared with standard grafts (58% vs 78%, p=0.007).[12] Our results showed that heparin-bonded grafts performed worse than standard grafts (44% vs 67% 1-year cumulative patency, p= 0.0001).[1] We speculated that selection bias affected our results.

There is a significant cost premium with heparin-bonded grafts compared to standard grafts. The 4-7mm tapered heparin-bonded graft costs Memorial Hermann Hospital $1185 versus $536 for the conventional tapered graft. If there is reduced incidence of thrombosis, there may be a significant cost benefit with more expensive graft material even without a difference in overall patency. Since patients receive ancillary care for access malfunction outside of hospitals where the access was created, e.g., free-standing access centers, we feel that a true estimate of the cost of functional graft patency must include all re-interventions. Because of the high incidence of recall bias in our patients, we will conduct monthly telephone queries regarding graft re-intervention. In addition to the healthcare cost of access re-interventions, the time spent on procedures and ancillary care can cause lifestyle disruption and adversely affect patient quality of life. We will administer a quality of life survey before surgery and at one- and two-year intervals to help determine the effect of access malfunction on a patient's perception

of their own health. A prospective randomized study would reduce selection and recall bias and allow a more accurate estimate of cost-benefit.

Primary Objectives

- *The primary objective of the study is to compare and contrast the efficacy of heparin-bonded PTFE (Propaten® or ACUSEAL®) versus the standard ePTFE vascular grafts for hemodialysis access.*

Primary Outcome Measures:

- *Primary patency rate.*
- *Primary-assisted patency rate.*
- *Secondary patency rate.*

Primary patency refers to the successful use of a vascular access for hemodialysis without any surgical or endovascular intervention. Primary-assisted patency is defined as a patent access with evidence of malfunction that requires an open surgical or endovascular intervention. A secondary or cumulative patency is defined as a functional access following intervention for thrombosis or after any interposition grafting for any reason including stenosis, aneurysm or pseudoaneurysm. The graft is considered abandoned when it is functionally unsalvageable or new replacement permanent vascular access is created. In cases where multiple interventions are required, the date of first intervention shall define the end of primary patency.

Secondary Objectives

- *To evaluate and compare the overall improvement in outcome with respect to morbidity, mortality and patient's quality of life.*
- *To compare and analyze the estimated costs with both types of graft interventions and their postoperative outcomes.*

Secondary Outcome Measures:

- *Complication or morbidity rates associated with both types of interventions.*
- *Number of postoperative reinterventions associated with both types of graft interventions.*
- *Cost estimation and analysis associated with both types of graft interventions including cost of*

graft, operation charges and readmission hospital and reintervention charges.

- *Change in patient perception of quality of life as measured by the SF-12v2® Health Survey Standard.*

Study Population:

The target population comprises of all adult patients aged 18 years and above with chronic kidney disease stage 4 (GFR 15-29 ml/min 1.73m^2) or stage 5 (GFR <15ml/min 1.73m^2) who require arteriovenous vascular access for hemodialysis and present as out-patient, in-patient or outside hospital/clinic referral during the 5 year course of the study. We will have an enrollment target of 200 patients over a period of 5 years.

Inclusion /Exclusion Criteria

Patients will be considered eligible if:

- *Aged ≥18 years of all ethnicities, and;*
- *Diagnosed with End-stage Renal Disease stage 4 (GFR 15-29 ml/min 1.73m^2) or stage 5 (GFR <15ml/min 1.73m^2) as per the National Kidney Foundation guidelines needing vascular access for hemodialysis; or,*
- *Currently undergoing hemodialysis with a failure of previous access; or,*
- *Expected to undergo hemodialysis within 6 months of presentation.*

Patients will be excluded if:

- *Unable or refuse to abide with follow-up; or,*
- *Known hypercoagulability syndrome or a bleeding disorder; or,*
- *Were on a previous anticoagulant treatment; or,*
- *Intraoperative decision was made in favor of fistula instead of graft; or,*
- *Pregnant or breast-feeding women; or,*
- *Patients with a documented history of heparin induced thrombocytopenia or allergy to heparin; or,*
- *Active infections; or,*
- *Evidence or suspicion of central vein stenosis but shall be included if a central vein catheter*

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or pacemaker is implanted as long as the patient had a venogram within past 6 months.

Withdrawal Criteria:

- *Voluntary: patients who had consented and enrolled in the trial will maintain their right to withdraw at any point during the study as explained in the informed consent.*
- *Failure to meet eligibility for graft implantation: The patient who had consented to participate in the trial might be considered ineligible for AVG implantation following intraoperative diagnostic evaluation and a decision for alternative vascular access is made instead.*
- *Failure to follow-up after multiple failed attempts of the research team to reach the patient. For statistical analysis, patients withdrawn from the study will be considered lost to follow-up and censored in the data analysis at the last known contact.*

Study Interventions:

Implantation of either of the two FDA-approved hemodialysis vascular grafts i.e. heparin-bonded polytetrafluoroethylene grafts (GORE PROPATEN® or ACUSEAL® Vascular Graft) vs. conventional expanded polytetrafluoroethylene grafts (GORE-TEX® Stretch Vascular Graft), are the two interventions under evaluation as part of this trial.

Device name: ***GORE PROPATEN® Vascular Graft***
Manufacturer/ Supplier of device: ***W.L. Gore and Associates***
FDA-Approved: ***Yes***

Device name: ***GORE*** *ACUSEAL®* ***Vascular Graft***
Manufacturer/ Supplier of device: ***W.L. Gore and Associates***
FDA-Approved: ***Yes***

Device name: ***GORE-TEX® Stretch Vascular Graft***
Manufacturer/ Supplier of device: ***W.L. Gore and Associates***
FDA-Approved: ***Yes***

The package and surgical handling of both the grafts is the same. However, the labeling that is

printed on the two types of grafts is different. The labeling and instructions on package provide detailed and clear information on storage conditions and "use by" label. There is no significant device level of risk. Any credentialed vascular surgeon can perform this procedure as per the standard graft implantation procedure.

Study Schedule:

Expected start date: October 1, 2012

Expected end date: December 31, 2017 or end of 24 month follow-up of last enrolled patient.

Length of enrollment per patient: 24 months from the time of graft implantation/enrollment.

Length of study: 5 years or time to the end of 24 month follow-up of last enrolled patient.

Follow-up period: 24 months.

Study design/methodology:

Study Type and Design:

- *This will be a prospective, multi-institution, parallel-group, single-blinded, randomized-controlled, two-arm, effectiveness study comparing heparin-bonded (Propaten® or ACUSEAL®) versus non-heparin-bonded arteriovenous grafts involving a patient population that requires a vascular access for hemodialysis. The target sample size will include enrollment of 200 patients over a period of 5years. The placement of either Propaten®/ ACUSEAL® or standard ePTFE vascular graft constitutes the two arms of the study.*

Arm 1	Heparin –bonded vascular hemodialysis graft implantation (*Propaten®/ ACUSEAL®)*
Arm 2	Standard ePTFE hemodialysis vascular graft implantation.

Following the graft implantation the patients will be followed-up as per the standard and study protocol for a period of 2 years from the time of graft implantation.

- *We will use block randomization to achieve a patient allocation ratio of 1:1, using varying*

blocks of sizes 4 and 6 in a random order as per a web-based/computer generated system maintained as a block randomization sequence/list concealed from the blinded clinical and trial research team until the end of trial. Patients will be randomly allocated based on this permuted sequence to either of the two intervention groups.

- *Masking will be performed and shall involve blinding of the patients participating in the trial. The research assistants involved with consenting, enrolling, data collection and follow-up, and the statistician analyzing the outcome measures will be blinded to the group assignment. The operating surgeon shall be blinded to the allocation process until the time of graft implantation following which the knowledge regarding the type of graft to the implanting surgeon is inevitable. Although the two different graft types handle and feel the same, the markings on the grafts are different and prevent blinding of the surgical team. Removing the markings is impractical since both grafts are FDA-approved and the labeling is required for commercial distribution.*

- *All patients will be consented and their study related details including history, physical evaluations, diagnostic tests, etc., will be entered on a case report form and maintained on a web-based database. The patients will be followed-up for a period of 2 years from the time of initial graft implantation until the graft is abandoned or rendered nonfunctional until the end of the study period.*

Study Conduct:

Screening:

The clinical study team or implanting surgeon will clinically examine the patient and determine the need for and type of hemodialysis access and the eligibility of the patient for inclusion into the study, based on the physical examination and pre-operative evaluation. If eligible a written, informed consent will be obtained from the patient after explanation of involved risks/benefits and alternatives that will authorize the surgeon to go ahead with graft implantation in case rendered necessary following intraoperative diagnostic evaluation. Case report forms will be completed by the research staff member of the study team.

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Quality of Life Assessment:

The SF-12v2® Health Survey Standard, is an externally-validated tool designed to measure self-reported quality of life. The SF-12v2® will be administered prior to scheduled surgery and at 1-year and 2-years postoperatively. It is designed such that patients of average intelligence and 6th-grade education should be able to complete the questionnaire of their own. Answers are in a check-box format. Patients with difficulty reading or who are physically unable to complete the questionnaire can be brought into a private exam room for verbal completion. The questionnaire consists of 80 disease-specific and general health questions. The areas of focus include: current symptoms, effect of renal disease on quality of life, effect on work, cognitive function, social interaction, emotional health, sexual function, sleep patterns, and general perception of health. It is estimated that the questionnaire will take 16 minutes to complete.

Enrollment:

Following the diagnostic evaluation and a decision for graft implantation made in the operating room, the pre-consented patient will be enrolled into the trial. At that time the study coordinator will be notified, the trial office will be contacted for allocation of the patient to an intervention group based on the random permuted-block design and a unique trial number will be assigned to the enrolled patient.

Randomization:

Randomization and allocation concealment will be performed via a web-based/computer generated block randomization sequence/list secured in a password-protected secure computer in the trial office accessible only to the research staff independent of the trial administration process, who is not involved in the recruitment, data collection, analysis, assessment or follow-up. This office/research staff will be contacted by the blinded research assistant/investigator and provide certain key details of the patient to be randomized that will be entered in the secure password protected computed-based entry system. The patient would then be allotted a trial number and allocated to a study arm group as per the randomized sequence list. In order to achieve the same distribution of subjects to each treatment arm and to maintain the design objectives, we will stratify based on the centers, i.e., have separate randomization lists

for each center following the same block randomization sequence.
All study sites will send the collected (de-identified) data to the primary study research office at the UT Cardiothoracic and Vascular Surgery that shall function as the data coordinating and analysis center. Strict confidentiality on randomized sequence list and allocated group will be maintained from all blinded participants of the study, including the patient, research staff involved with consenting, recruiting, data collection, follow-up, data assessment and analysis and the surgeon/investigator (up to the point of graft implantation).

Follow-up:

Following the implantation of the graft, all patients will be followed-up as per the standard postoperative follow up with the primary clinical team consisting of first scheduled out-patient clinic visit 15 days post graft implantation, followed by once every 3months for a total of 24 months post graft implantation. A surveillance program specific to the trial shall include a phone call made by a research staff to the patient once every month (excluding the month of a scheduled clinic follow-up visit) in addition to the standard follow-up protocol. During the follow-up visit the patient will undergo an assessment of graft patency through standard physical examination, evaluation of pain during dialysis associated with the graft implantation, evaluation of adverse events, documentation of medications that the patient is taking, any access related readmissions to an outside hospital or clinic, patient's quality of life, and an annual surveillance duplex scan. Duplex scans may be obtained at the clinician's discretion at any follow-up encounter. The patient will be educated on the importance of reporting any adverse events that may be a result of primary or secondary outcomes to the procedure. Definitions and examples of adverse events will be documented and given to the patient for reference as well as contact information to the office to speak to someone about documenting these adverse events. The monthly follow-up call conducted by the research staff shall be directed on obtaining information regarding the graft patency and questions similar to the following will be asked:

1. *"Did you have any problems with dialysis access since your last follow-up?"*
2. *"Do you have any pain associated with the graft?"*
3. *"Did you have any drainage, open wounds, or bleeding issues with respect to the graft site?"*

4. *"Are you currently taking any new medications? If so, list them."*
5. *"Did you have any hospitalizations or procedures related to graft malfunction in the past 1 month?"*

   If yes then,

   a. When was the patient readmitted?

   b. Was a vascular re-intervention performed?

   c. What was the reintervention?

   d. What was the reason for reintervention?

   e. Details on the procedure, with respect to date, time of hospitalization, cost of procedure, admission and hospital stay.

In case of a yes to Q. 5, encourage a visit to office for a clinical examination.

Follow-up Graft Evaluation

Patency of the grafts will be assumed if the patient continues to receive successful hemodialysis. Duplex surveillance of the grafts will be performed annually at the least. However, in the event of clinical evidence of deterioration in graft function, such as decreased flows on hemodialysis as reported by the dialysis center or loss of thrill or bruit on physical examination during the patient's scheduled clinic visits, further investigation either by duplex or angiography may be ordered at the physician's discretion. Treatment of infection, pseudoaneurysm, clinically-significant stenosis, or other causes of graft dysfunction will follow the practice standard. Treatment of dysfunctional grafts will be determined by the patient's surgeon and may require endovascular or open surgical revision as appropriate.

The protocol for sonographic evaluation of the grafts will follow the current practice standard. All duplex scans will be performed by Registered Vascular Technologists who are members of an ICAVL accredited laboratory. Peak systolic velocities will be assessed in the inflow artery, along the length of the graft, and at the venous and arterial anastomoses. Greyscale and color Doppler images are routinely obtained. All duplex scans will be interpreted by approved physicians of the vascular laboratory. Those patients determined to have clinically-significant stenosis or other graft dysfunction will be referred for intervention as per the practice standard.

1-Year Quality of Life Assessment

At 1-year postoperatively, the SF-12v2® will again be administered.

Final Visit with Quality of Life Assessment:

The final study visit will be 24 months following the graft implantation and will follow the same format as the previous follow-ups. The SF-12v2® will be administered just prior to termination of enrollment at the last study office visit. A duplex ultrasound will be obtained. Patients may continue to follow-up per surgeon preference after termination of enrollment. Termination of enrollment does not entail severance of the physician-patient relationship.

Termination of Enrollment:

The patient participation in the trial will terminate under the following circumstances:

- *Abandonment of the graft (functionally unsalvageable or new replacement permanent vascular access is created).*
- *Death of the patient.*
- *End of 24 month follow-up period.*
- *Termination of the study.*

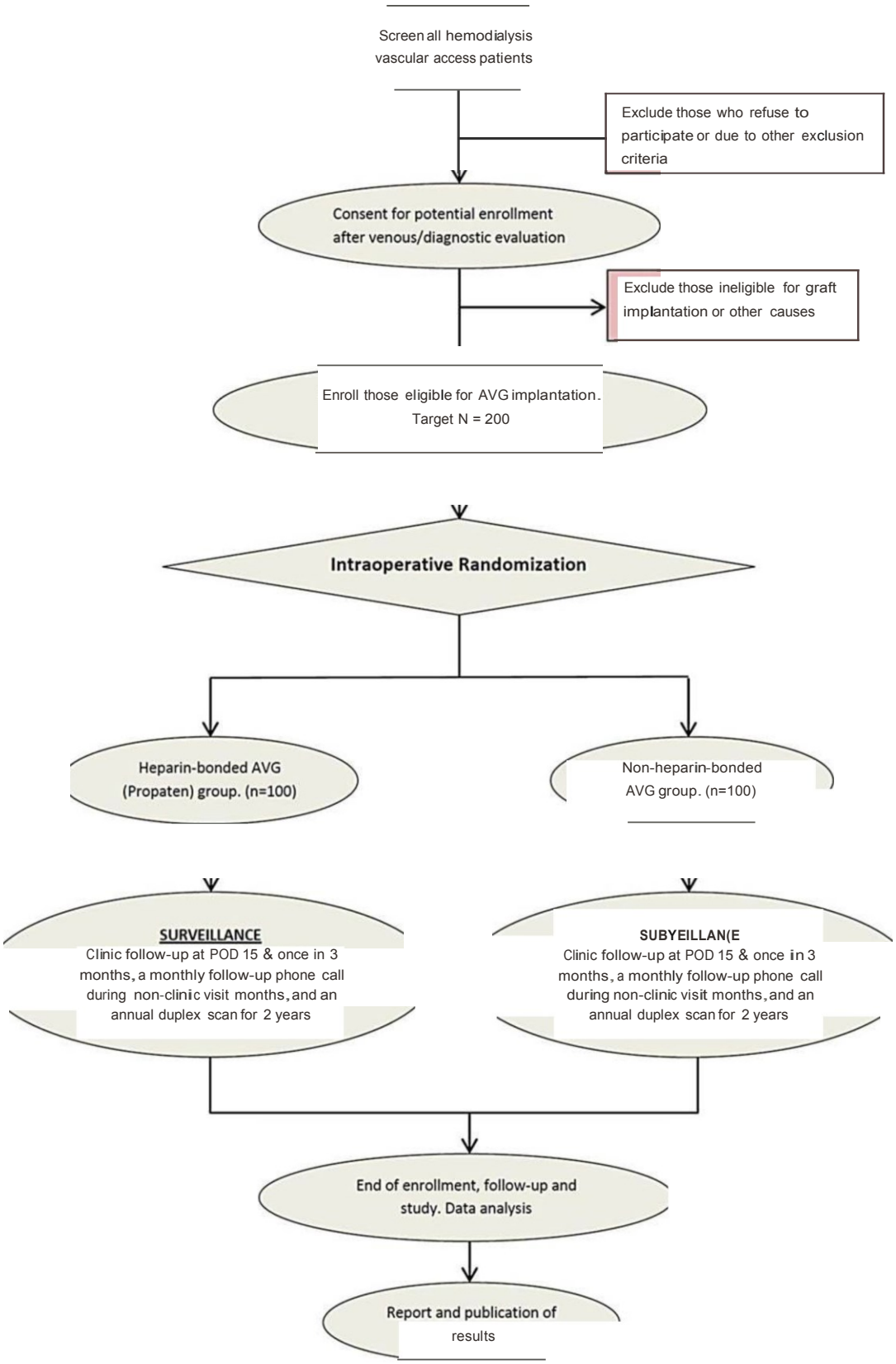
Methodological Steps:

1. *Clinical assessment of the patient for the need and type of vascular access (AVF vs AVG) for hemodialysis in outpatient clinic or in-patient setup.*
2. *Screening of patients based on inclusion and exclusion criteria.*
3. *Obtaining an informed consent after explanation of involved risks/benefits and alternatives. Since the decision on type of access, i.e. fistula versus graft is sometimes made following an intraoperative diagnostic procedure, the patient will be consented in advance in lieu of a potential enrollment. Pre-operative data will be recorded on a case report form and entered into the electronic database.*
4. *Quality of life questionnaire (SF-12v2®)*
5. *Diagnostic evaluation and final decision regarding (AVF vs. AVG) graft implantation based on intraoperative venogram or preoperative vein mapping.*

6. *If graft is to be implanted, study coordinator will be notified at 713-486-5120.*
7. *Patient is enrolled into the trial.*
8. *The trial office will be contacted for randomized intervention group allocation to the patient enrolled and a trial number will be assigned.*
9. *Implantation of allocated graft by credentialed surgeon.*
10. *A surveillance program consisting of a standard postoperative follow up and an additional monthly phone call made by a study research staff shall be implemented.*
11. *Patency of the grafts will be assumed if the patient has successful hemodialysis on surveillance. In addition, a duplex scan of the grafts will be performed at least once a year or more per physician's discretion.*
12. *Quality of life questionnaire at 1-year postoperative visit (SF-12v2®).*
13. *Quality of life questionnaire at 2-year postoperative visit (SF-12v2®).*
14. *Termination of enrollment at 2 years after graft implantation.*

A graphical representation of study steps is provided below:

Trial Profile following CONSORT guidelines



Adverse Event Reporting:

During each scheduled follow-up visit, the patient will be educated on the importance of reporting any adverse events that may be a result of primary or secondary outcomes to the procedure and assessed for patency of the graft through physical examination looking for an absent bruit or thrill, evaluation of pain during dialysis associated with the graft implantation, evaluation of adverse events, documentation of medications that the patient is taking, any access related readmissions to an outside hospital or clinic, patient's quality of life, and an annual surveillance duplex scan. Definitions and examples of the standard or known adverse events associated with AVG implantation like thrombosis, infections, pseudoaneurysms, hematoma, central venous stenosis, etc., along with their documented percentage/ annual risk of occurrence will be presented to the patient for reference. In addition, emergency contact information of the office in order to speak to someone regarding documentation of these adverse events will be provided. If need be, an immediate unscheduled visit shall be arranged if the patient so desires.

Statistical Analysis Plan:

Primary Outcomes:

Separate univariate Kaplan-Meier analyses will be conducted for each of the primary endpoints (primary patency, primary-assisted patency and secondary patency). Failure endpoints will be reached at the first event of each type. If a participant withdraws, is lost to follow-up, or dies during follow-up, the last known event or censoring at the last known time will be taken as the final endpoint for statistical analysis. Randomization is expected to balance the groups with respect to preoperative risk factors, but if major imbalances occur that require adjustment, we will use Cox regression, and will present adjusted and unadjusted analyses together in publications. Adjustment for post-randomization events or changes in risk factor profiles will not be performed.

Secondary Outcomes:

Indicators of incident morbidity and mortality that occur on-study will be compared using relative risk or repeated-measures analysis of variance techniques as appropriate for the type and distribution of data. Where continuous data are not normally distributed, meaningful

transformations will be used preferentially to non-parametric methods. SF-12v2® Health Survey© will be scored according to published scoring rubric [13]. Change over time will be assessed by simple two-way repeated-measures ANOVA. If other covariates must be taken into account to interpret the SF-12v2® Health Survey©, mixed model analysis will be employed.

Sample size determination

We aim to enroll 200 patients to achieve a statistical power of 80% with a two-sided risk of type 1 error of 5% in order to justify the existing scientific data that reports a 20% improvement in graft patency or the primary outcome and for detecting a statistically significant difference with a p-value of < 0.05. The rationale for these calculations is based on the reported 78% and 58% graft patency rate at the end of one year in heparin-bonded grafts and non- heparin-bonded grafts, respectively, in a recent non-randomized trial conducted in dialysis patients. Assuming the usual rates of error, α = 0.05 and β = 0.20, 85 patients would be needed per group. Since compliance to follow-up will affect the primary outcome measure, we have taken into consideration a 10% withdrawal and loss-to-follow/up rate and the total sample size has been set to 200 patients. This number will account for missing and spurious data along with cases that failed to comply with study design and yet not significantly affect the outcome measures.

Ethics

Informed Consent Process:

The patients who will meet the inclusion criteria and considered eligible for participation in the trial will be consented for their willingness to participate in the study after a detailed description of the research study in terms of its purpose, procedure, period of commitment, risks and benefits of the study along with of the two types of interventions or grafts, and the need, conduct and duration of follow-up. Since the final decision on type of access, i.e. fistula versus graft would be made following an intraoperative diagnostic procedure like a venogram or a venous mapping, the patient will be consented in advance in lieu of a potential enrollment. The only potential risk of enrollment is inadvertent disclosure of patient's protected health information. The patients will not incur any extra cost over the standard treatment and since both the devices/grafts are FDA approved, any difference between the costs of either of the graft/device will be covered by their insurance.

All this information will be clearly communicated both verbally and through a written consent form structured in detail in English (and Spanish) at a 6th grade level of understanding. Consenting or enrollment will not obligate the patient to go through with the study, although the need for follow-up will be emphasized but the decision to not participate or end participation at any point in time will be under the absolute voluntary control of the patient. Assurance will be given regarding maintenance of patient confidentiality, de-identification of the data collected and that non-participation shall not change the standard or quality of treatment and care provided in any way. A copy of the signed consent shall be provided to the patient.

Privacy and confidentiality:

The study shall be conducted in strict compliance with the HIPAA guidelines in order to protect patient confidentiality. All sensitive information or patient identifiers will be stored in form of a patient linkage file that will link the patient study/trial number to their clinical records and secured on the Zone 100 drive on specific networked computers of our department. We will create a password protected electronic database that, along with the case report forms, will be de-identified and contain only study relevant data points and the patient's trial number. All study sites will collaborate to maintain data safety and integrity in a uniform fashion and will send the de-identified data to the primary study research office at the UT Cardiothoracic and Vascular Surgery that shall function as the data coordinating and analysis center. Access to any data pertaining to the study will be restricted to approved research team members, the FDA, institutional review boards. Case report forms will be shredded and the linkage file erased and destroyed 5 years after the conclusion of the study.

Risk/Benefit:

Risk to participants:

Since this study involves use of the standard-of-care and FDA-approved grafts and interventions, we do not expect any additional physical risks that the patients might encounter. The only discernible risk involved is an unintentional disclosure of sensitive patient health information.

Benefits to Participants

The participants of this study do not stand to benefit directly from taking part; however, we hope

that the results obtained from this study would provide useful information that would help delineate a standard and economical protocol for vascular access in hemodialysis patients in future.

Study Timeline:

At present, our department performs 8 vascular access cases at an average per month. As per this estimate, we hope to accrue our target trial sample size in 3 years keeping under consideration a slow rate of enrollment, patient drop-outs or refusal to consent/participate, etc. Given an additional 2 years of follow-up period, we hope to finish the study in the speculated period of 5 years. The results of the study shall be presented/published as soon as possible after the completion of trial and statistical analysis.

Stage 1: Patient screening and enrollment (years 0-3)

Stage 2: Follow-up and surveillance (years 0-5)

Stage 3: Data collection and analysis (years 3-5)

Stage 4: Presentation of results and publication

Data Safety Monitoring:

An independent data safety monitoring committee consisting of members not directly involved with the study design and conduct will perform the data safety monitoring for this study. In addition, the Principal Investigator of this study, Dr. Charlton-Ouw from the Department of Cardiothoracic and Vascular Surgery at The University of Texas at Houston Medical School, will annually meet with other co-investigators to review the patients enrolled in this study. As part of the data safety monitoring plan, all patients enrolled until that point in time would be unblinded in order to review the outcomes.

Interim analyses will be conducted at the one-year follow up time point of the 66th and 133rd patient using a group-sequential design. If one product is demonstrably inferior to the other using a three-stage group-sequential overall nominal value of 0.05 (alpha spending of 0.007, 0.022 and 0.042 at 66, 133 and 200 participants accrued, respectively [14], the study will be stopped early and

the results will be reported to the IRB and published.

Conflict of Interest:

Drs. Charlton-Ouw was formerly a consultant for W.L. Gore and Associates. Dr. Charlton-Ouw receives research funding from Cook Medical. Dr. Azizzadeh is a consultant for Gore and Medtronic. Such funding or consulting will not involve or affect the conduct of this study.

Publication and Presentation Plans:

The results of this study will be analyzed and published after the approval of the principal investigator, co-investigators, and biostatistician in a peer-reviewed scientific journal and/or presented at an international/national scientific conference or meeting regardless of outcome. The publication will list all members of the study research group for their contributions and will maintain patient data protection.

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