Statistical Analysis Plan

Study Acronym / Protocol #: HVG 13-01
Table of Contents

1. Introduction .............................................................................................................. 4
2. Study Design Overview .......................................................................................... 4
   2.1. Objectives ....................................................................................................... 4
   2.2. Design Summary ............................................................................................. 5
   2.3. Study Endpoints .............................................................................................. 5
       2.3.1.10. ........................................................................................................ 6
       2.3.1.9. ........................................................................................................ 6
       2.3.1.8. ........................................................................................................ 6
       2.3.1.5. ........................................................................................................ 6
       2.3.1.4. ........................................................................................................ 6
       2.3.1.1. ........................................................................................................ 6
2.4. Potential Risks ..................................................................................................... 7
2.5. Randomization Scheme ..................................................................................... 7
2.6. Blinding Scheme ................................................................................................ 8
2.7. Statistical Hypotheses ....................................................................................... 8
2.8. Sample Size Assumptions ................................................................................ 8
2.9. Sample Size Calculations ................................................................................ 8
3. Study Treatment Arms ............................................................................................ 8
   3.1. Test Arm ......................................................................................................... 8
   3.2. Control Arm ................................................................................................... 8
4. Study Data Collection .............................................................................................. 9
   4.1. Enrollment ....................................................................................................... 9
   4.2. Follow-Up Intervals ....................................................................................... 9
5. Statistical Analyses ................................................................................................. 9
   5.1. Timing of Analysis ......................................................................................... 9
   5.2. Analysis Population ....................................................................................... 9
   5.3. Primary Endpoints ......................................................................................... 10
   5.4. Additional Assessments ............................................................................... 10
   5.5. Comparison of baseline characteristics ....................................................... 10
   5.6. Adverse Events ............................................................................................. 10
   5.7. Pooling of Data ............................................................................................ 11
5.8.  Sub-group Analysis:.............................................................................................................. 12
6.  Analysis Specifications .............................................................................................................. 12
   6.1.  SAS Analysis Dataset Specifications ................................................................................. 12
   6.2.  Statistical Output Specifications ......................................................................................... 12
   6.3.  Verification Level for Statistical Output ............................................................................ 12
7.  Data Sets, Tables, Figures, and Listings ..................................................................................... 12
   7.1.  Analysis Tables .................................................................................................................. 12
   7.2.  Analysis Listings ............................................................................................................... 13
   7.3.  Analysis Figures ................................................................................................................ 14
   7.4.  Analysis Data Sets ............................................................................................................ 14
8.  References .................................................................................................................................... 14
1. Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of HVG 13-01. This SAP summarizes the analyses that will be performed to characterize the safety and efficacy of 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). This SAP exhibits tables, figures, and listings that will be prepared as part of the final study report.

2. Study Design Overview

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.

Subjects may continue into the extended portion of this clinical study (post Day 90) provided that they have re-consented and the vascular graft has not been abandoned. Subjects will be evaluated post Day 90 and return for follow-up visits at Month 6 and Month 12.

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, adverse events, and revisions to the circuit
- **Day 90 (±14 days)** – Collection of blood and serum samples, adverse events, and revisions to the circuit
- **Month 6 (±14 days)** - Duplex ultrasound measurements, adverse events, and revisions to the circuit
- **Month 12 (±14 days)** - Duplex ultrasound measurements, adverse events, and revisions to the circuit

2.1. Objectives

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).
2.2. Design Summary

Screening Inclusion & Exclusion Criteria  
Randomization (n=200) 1:1  
100 in each arm

Test Arm: GORE® Hybrid Vascular Graft

Control Arm: Non-Heparin bonded synthetic graft

Follow-Up: Day 7, 14, 30, 90; Month 6 and 12

2.3. Study Endpoints

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

2.3.1. Additional Assessments

2.3.1.1. Anti-PF4/H antibody seroconversion

Seroconversion is defined as a positive Serotonin Release Assay (SRA), positive IgG-specific Enzyme Immunoassay (EIA), and / or positive poly-specific EIA at either / both of Day 7 and Day 14 time points in relation to a corresponding negative baseline (t_0) result [minimum, 30.0% increase in OD from baseline], analyzed individually for each of the three assays (SRA and the two EIAs).

For the SRA, a seroconversion specifically means a change from a negative baseline to a positive result (defined subsequently) at Day 7 and / or Day 14 (note: a corroborating EIA seroconversion would be expected in the event of an SRA seroconversion).
A subject who has a positive baseline EIA would be considered to exhibit seroconversion if either of both of their Day 7/14 samples showed at least a 2-fold [>100%] increase in OD for either of the EIAs.

2.3.1.2. Anti-PF4/H antibody late seroconversion
Late seroconversion is defined as a positive SRA, positive IgG-specific EIA, and/or positive polyspecific EIA at either of both of the Day 30 and Day 90 time points in relation to corresponding negative results at baseline (Pre-Procedure), Day 7, and Day 14 [minimum, 30.0% increase in OD from baseline], analyzed individually for each of the three assays (SRA and the two EIAs).

For this secondary analysis, high heparin inhibition is not required for defining an EIA seroconversion.

2.3.1.3. Anti-PF4/H antibody seroreversion
For IgG or polyspecific EIA: (Positive at T0, T7, or T14) and ((Negative at T30 or T90) or (Positive T30 and T90 with >=50% decrease in OD units from higher of T7/T14))
For SRA: (Positive at T0, T7 or T14) and (Negative at T30 or T90)

2.3.1.4. Prevalence of a positive IgG-specific EIA
For IgG or polyspecific EIA: Positive at either Day 7 or Day 14 time points

2.3.1.5. Prevalence of a positive SRA panel
Positive SRA at either Day 7 or Day 14 time points

2.3.1.6. Platelet Count
Platelet counts at pre-procedure, Days 7, 14, 30, and 90 time points

2.3.1.7. Volume flow in circuit and venous diameter
Volume flow in circuit and venous diameter measurements determined by duplex ultrasound post-Index Procedure at Day 30, Day 90, Month 6, and Month 12.

2.3.1.8. Primary Patency
The primary unassisted/uninterrupted patency is defined as a subject free from the occurrence of either access thrombosis or an access procedure to maintain access patency. The primary patency will be presented using Kaplan Meier curves up to 12 months and compared between the two study arms using log-rank test.

2.3.1.9. Cumulative Patency
Defined as a subject free from complete loss of access for hemodialysis at the study access site regardless of number of interventions required to
2.4. 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:

<table>
<thead>
<tr>
<th>Infection Graft (early)</th>
<th>Infection Graft (late)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm edema</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Pseudoaneurysm</td>
</tr>
<tr>
<td>Access-related Limb Ischemia (Steal Syndrome)</td>
<td>Congestive Heart Failure</td>
</tr>
<tr>
<td>Anastomotic Disruption</td>
<td>Perigraft Hematoma</td>
</tr>
<tr>
<td>Infection</td>
<td>Device deployment failure</td>
</tr>
<tr>
<td>Arm edema</td>
<td>Perigraft Seroma</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Device fracture</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>Pseudoaneurysm</td>
</tr>
<tr>
<td>Access-related Limb Ischemia (Steal Syndrome)</td>
<td>Congestive Heart Failure</td>
</tr>
</tbody>
</table>

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 nitinol reinforced section of the GHVG. All other aspects of the vascular graft are equivalent.

2.5. Randomization Scheme
The randomization will be organized using randomization envelopes. Subjects will be stratified by Site and will be considered randomized as soon as the randomization envelope is opened after determining the eligibility for inclusion in the study. Any irregularity in the randomization process will be documented and reported to the Sponsor.
2.6. **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. Only overall statistical reports without the identification of the study arm will be available during the conduct of the study.

2.7. **Statistical Hypotheses**

The hypothesis is specified as follows:

\[ H_0: \text{Prevalence of anti-PF4/H antibodies on GORE® Hybrid Vascular Graft} \geq 0.15 \text{ versus } H_1: \text{Prevalence of anti-PF4/H antibodies on non-heparin grafts at Day 7 and/or Day 14 < 0.15}, \]

where \( P_H \) = Prevalence of anti-PF4/H antibodies on GORE® Hybrid Vascular Graft and \( P_N \) = Prevalence of anti-PF4/H antibodies on non-heparin grafts at Day 7 and/or Day 14.

2.8. **Sample Size Assumptions**

The sample size approach used for the study is for testing the non-inferiority hypothesis. An absolute margin of up to 15% excess is considered clinically acceptable. This implies the GORE® Hybrid Vascular Graft would be deemed to have shown non-inferior to the control in terms of the anti-PF4/H antibodies positive prevalence, if the upper bound of the 95% confidence interval of the difference between proportions \( (P_H - P_N) \) stays below 0.15. The assumption is the prevalence of antibodies in the control arm would be less than 15%.

2.9. **Sample Size Calculations**

The sample size is calculated using PASS 12 software based on test for the difference of proportions. With the one-sided level of significance of 2.5%, prevalence of less than 15% on non-heparin graft and an absolute non-inferiority margin of 15%, a total of 100 subjects per arm are required to rule out inferiority of GORE® Hybrid Vascular Graft with at least 80% power.

3. **Study Treatment Arms**

3.1. **Test Arm**

GORE® Hybrid vascular graft

3.2. **Control Arm**

Non-heparin bonded synthetic vascular grafts
4. Study Data Collection

4.1. 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. Case report forms will still be completed to reflect screening activities, procedure, and discontinuation. Pre-procedure blood and serum samples should be shipped to Covance for processing.

4.2. Follow-Up Intervals
There are four (4) 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)

5. Statistical Analyses

5.1. Timing of Analysis

5.2. Analysis Population

5.2.1. 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.

5.2.2. As Treated
“As treated” population is defined as all Subjects analyzed by type of the actual implanted device.
5.3. **Primary Endpoints**

The primary analysis will be performed as difference of proportions ($P_H - P_N$) in the two arms. The 95% Confidence Interval of difference will be constructed using standard normal distribution. If the upper bound of the confidence interval is below 0.15 that would result in rejection of the null hypothesis and conclusion that the **GORE® Hybrid Vascular Graft** is not inferior to the non-heparin coated synthetic graft by more than 15%.

5.4. **Additional Assessments**

There is no specific hypothesis for the additional assessments. The results will be presented as frequencies and percentages for the categorical and will be presented as means and standard deviations for the continuous or quantitative variables for all additional assessments of interest.

5.5. **Comparison of baseline characteristics**

Due to the randomization, any difference in the baseline characteristics observed between the two arms is expected to be due to chance alone. Therefore, no formal statistical testing will be done to test if the baseline characteristics differ by more than what would be expected by chance.

5.6. **Adverse Events**

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

5.6.1. **Anticipated Adverse Events**

Anticipated AEs are complications that are known to be associated with hemodialysis patients undergoing the creation of vascular graft access.

The Sponsor considers occurrences of thrombosis and stenosis to be efficacy outcomes and not AEs. These occurrences should be reported on a Revision to Circuit Case Report Form (CRF): Should there be clinical sequelae associated with thrombosis and stenosis, these sequelae are considered AEs and should be reported.

5.6.2. **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.

5.6.3. **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.

5.7. **Pooling of Data**
Data will be pooled from all Sites participating in the study. To help ensure homogeneity of data across Sites, the protocol will be administered and monitored in a uniform manner at all Sites.
5.8. **Sub-group Analysis:**

Subgroup analysis of Primary and other key patency outcomes only will be assessed for differences of treatment effect between sex by including interaction term consisting treatment and sex in the model that already contains treatment and sex as main effects. If the interaction term is significant at 0.1 level of significance then the analysis will be presented separately by sex.

6. **Analysis Specifications**

6.1. **SAS Analysis Dataset Specifications**

A specifications document will be created for each analysis data set that will contain, at a minimum:

- Variable Name
- Format
- Label
- Input Fields

6.2. **Statistical Output Specifications**

A specifications document will be created for each statistical output (Table, Listing, or Figure) that will contain, at a minimum:

- Title and footnote information
- Column headers
- General appearance of each cell (table, listing)
- If the spec includes a figure, either an example figure or a detailed description of the figure is included in this section
- Variables used in statistical output
- Change log section

6.3. **Verification Level for Statistical Output**

- The Analysis Datasets, Tables and Listings will be validated using the following levels as defined in the MD111325.
- All Analysis Datasets – Level I
- All Tables – Level I
- All Listings – Level II

7. **Data Sets, Tables, Figures, and Listings**

At a minimum, the following set of Tables, Figures, and Listings will be produced for both arms separately and combined together. Unless specified, the population for all tables is the “Intent-to-Treat”.

7.1. **Analysis Tables**

- Subject Demographics
• Subject Physical Exam
• Subject Lab Results
• Subject Medical History
• Anticoagulant and/or antiplatelet therapies within the past 6 months
• Summary of Enrollment by Site
• Summary of Vascular Access History
• Summary of Device Use
• Summary of Procedural Assessments
• Subject Status/Reason for Withdrawal
• Summary of positive poly-specific enzyme immunoassay (EIA)
• Summary of Anti-PF4/H antibody seroconversion
• Summary of Anti-PF4/H antibody seroreversion
• Summary of positive IgG-specific EIA at Day 7 and / or Day 14
• Summary of positive full serotonin release assay (SRA) panel
• Summary of platelet count at Pre-procedure, Day 7, 14, 30, and 90
• Summary of Cumulative Patency at Month 6 and 12
• Kaplan-Meier Estimates of Cumulative Patency
• Kaplan-Meier Estimates of Primary Patency
• Summary of All Adverse Events by MedDRA SOC, PT

7.2. Analysis Listings
• Listing of Deaths
7.3. Analysis Figures

- Time to Loss of Primary Patency
- Time to Loss of Cumulative Patency

7.4. Analysis Data Sets

- A_ELIG
- A_DEMO
- A_MEDHX
- A_VASCHX
- A_PROCEDURE
- A_FU
- A_BLOOD
- A_ULTRASOUND
- A_REVISION
- A_AE
- A_COMP_DISC
- A_OUTCOMES

8. References

...