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
[redacted] 5
[redacted] 6
[redacted] 6
[redacted] 6
[redacted] 6
[redacted] 6
[redacted] 6
[redacted] 6
[redacted] 6
[redacted] 7
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 term 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.

[redacted]

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.

[redacted]

Follow up Schedule

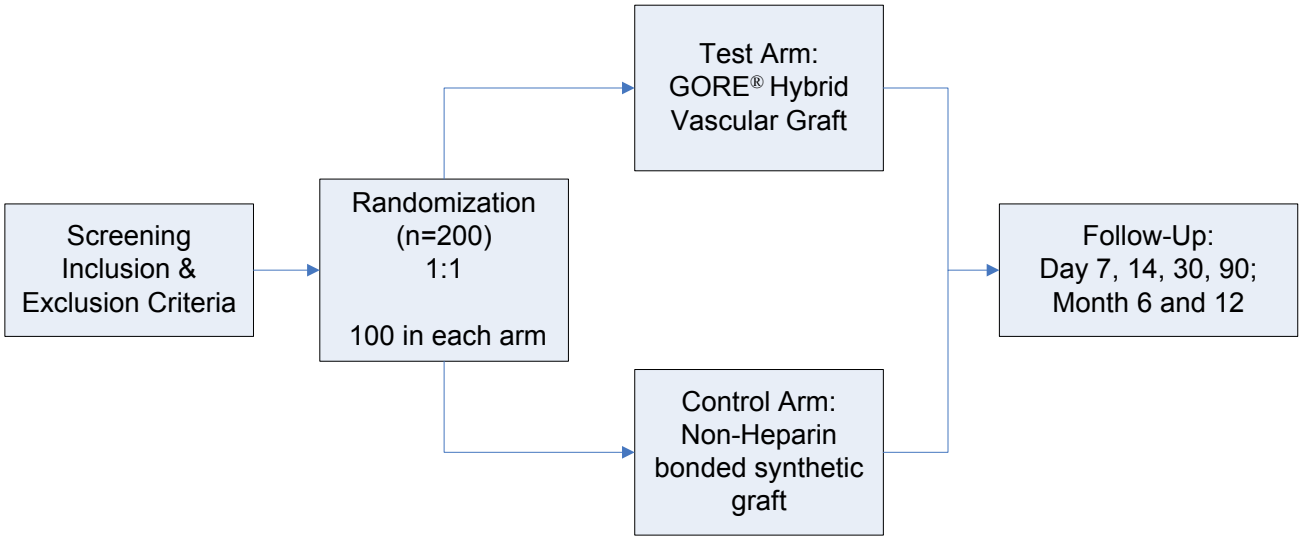
- **Day 7 (±2 days) -** Collection of blood and serum samples, adverse events, and revisions to the circuit
- **Day 14 (±2 days)** – Collection of blood and serum samples, adverse events, and revisions to the circuit
- **Day 30 (±7 days)** – Collection of blood and serum samples, [redacted], adverse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

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).

[redacted]

2.2. Design Summary



2.3. Study Endpoints

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

[redacted]

[redacted]

[redacted]

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:

[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 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 [redacted]. [redacted] 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

[redacted]

The hypothesis is specified as follows:

[redacted]

2.8. Sample Size Assumptions

[redacted]

2.9. Sample Size Calculations

[redacted]

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 [redacted]

[redacted]

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

[redacted]

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.

[redacted]

5.3. Primary Endpoints

[redacted]

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.

[redacted]

5.8. Sub-group Analysis:

[redacted]

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 [redacted].
- 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 [redacted]

- Subject Physical Exam [redacted]
- Subject Lab Results [redacted]
- Subject Medical History [redacted]
- Anticoagulant and/or antiplatelet therapies within the past 6 months [redacted]
- Summary of Enrollment by Site [redacted]
- Summary of Vascular Access History [redacted]
- Summary of Device Use [redacted]
- Summary of Procedural Assessments [redacted]
- Subject Status/Reason for Withdrawal [redacted]
- Summary of positive poly-specific enzyme immunoassay (EIA) [redacted]
- 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 [redacted]
- Summary of All Adverse Events by MedDRA SOC, PT

7.2. Analysis Listings

- Listing of Deaths [redacted]

[redacted]

- Listing of Study Completion / Discontinuation Data
- Listing of All Adverse Events

[redacted]

- Listing of Inclusion / Exclusion Criteria Violations

[redacted]

7.3. Analysis Figures

[redacted]

7.4. Analysis Data Sets

[redacted]

8. References

[redacted]