Statistical Analysis Plan

Study Acronym/Protocol #: AAA 13-02

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the GORE® EXCLUDER® Thoracoabdominal Branch Endoprosthesis study (AAA 13-02). This SAP summarizes the analyses that will be performed for the initial assessment of the feasibility of the GORE® EXCLUDER® Thoracoabdominal Branch Endoprosthesis (TAMBE Device) for treatment of aortic aneurysms involving the visceral branch vessels. This SAP outlines tables, figures, and listings that are included in reports for the AAA 13-02 clinical study.

2.0 Study Design Overview

2.1 Primary Objective

The primary objective of the GORE® EXCLUDER Thoracoabdominal Branch Endoprosthesis study (AAA 13-02) is to provide an initial assessment of the feasibility of the TAMBE Device in the treatment of aortic aneurysms involving the visceral branch vessels.

2.2 Design Summary

The AAA 13-02 study will be a prospective, nonrandomized, multicenter, single-arm evaluation designed to provide an initial assessment of the feasibility of the TAMBE Device in the treatment of aortic aneurysms involving the visceral branch vessels. Six sites in the United States and one site in Brazil, and an estimated maximum of 20 subjects treated with the TAMBE Device will participate in this study. Subjects may be enrolled into the clinical study provided all inclusion/exclusion criteria are met. Subjects will be evaluated through hospital discharge and return for follow-up visits at one (1), six (6), 12, 24, 36, 48 and 60 months. Subject accrual is anticipated to be 18 months.

2.3 Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint of the study will be procedural safety defined as the absence of the following events through 30 days post-procedure:

- Death
- Stroke
- Myocardial Infarction
- Bowel Ischemia
- Paraplegia
- Respiratory Failure
- Renal Failure
- Procedural Blood Loss ≥1000 mL

These events will be adjudicated to the definitions provided in Appendix A of the protocol by a CEC.

2.3.2 Secondary Endpoints

Secondary endpoints include the following:

- Technical Success, including individual components of technical success
- Device Integrity, including Individual components of device integrity
- Patency (Primary, Assisted Primary, and Secondary)
- Absence of Type I and Type III endoleaks at one month follow-up

Technical success is defined as:

- Successful access to the necessary arterial sites
- Successful deployment of all required TAMBE Device components and any required accessory components
- Patency of all required TAMBE Device components and any required accessory components on completion angiography
- Absence of surgical conversion within 24 hours of initiation of the procedure

Device integrity will be defined as freedom from all of the following events in the first year of follow-up.

- Loss of functional patency in any treated branch component due to thrombus or mechanical failure of the branch component
- Loss of functional patency in the main body component(s) due to thrombus or mechanical failure of the main body component(s)
- Separation of the treated branch components from the main body component(s)
- Separation of the main body component(s) from the accessory components (Distal Bifurcated Component Device and / or Contralateral Leg Components)

The definitions for device integrity in Appendix A of the protocol were based on the proposal outlined in Chaikof et al.[1]. These events will be adjudicated by a CEC. Device integrity and its individual components will be reported at interim follow-up time points as well, including one and six months.

Patency will be assessed using Kaplan-Meier analysis. Subjects not experiencing an event will be censored at time of last follow-up or contact. Subjects having events are defined below:

- Primary patency - Blood flow without occlusion maintained through the device after implant without an intervention. Subjects who have a reintervention on a treated segment before occlusion to prevent eventual loss of patency, after occlusion to restore patency, or open surgical bypass to restore patency will have lost primary patency at the earliest such reintervention.

- Assisted primary patency - Blood flow maintained through the device after implant regardless of re-interventions performed (without occlusion). Subjects who have a reintervention on a treated segment after occlusion to restore patency, or open surgical bypass to restore patency will have lost assisted primary patency at the earliest such reintervention.
- Secondary patency - Blood flow through the device (following occlusion) regardless of re-interventions performed and freedom from surgical bypass. Subjects who have open surgical bypass to restore patency of a treated segment will have lost secondary patency at the earliest such reintervention.

2.4 Statistical Hypotheses

No formal hypothesis tests will be performed.

3.0 Study Treatment Arms

3.1 Test Arm

Patients with thoracoabdominal or pararenal abdominal aortic aneurysms are eligible for screening for participation in the study. The particular characteristics of the patient's aneurysm and anatomy will determine ultimate eligibility for enrollment. 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 eligibility criteria will be enrolled. Anatomic criteria will be verified by the Sponsor prior to enrollment.

3.2 Control Arm

There is no control arm in this clinical study.

4.0 Study Data Collection

4.1 Study Data Collection Intervals

At the time of hospital discharge, Subjects will undergo a physical exam, a blood draw for general clinical health including BUN / Creatinine concentration and an abdominal ultrasound (optional).

Following hospital discharge, Subjects will be asked to return for follow-up visits at one month, six months, and annually for five years post-treatment. At each of these follow-up visits, Subjects will undergo an evaluation for adverse events. Evaluation methods will include a physical examination, a blood draw for BUN / Creatinine concentration, per-imaging guidelines spiral CTA of the abdomen and pelvis, and abdominal ultrasound (optional). Magnetic Resonance Angiogram (MRA) may be used as a follow-up imaging modality if the Subject is contraindicated for the required CTA follow-up. Table 1 outlines the required procedures at each follow-up visit.

Table 1: Subject Follow-up Schedule

	Pre-Treatment	Treatment	Hospital Discharge	One Month	Six Months	Annually through 5 Years
Physical examination	X		X	X	X	X
Spiral CTA (contrast)*	X			X	X	X
Spiral CT (non-contrast)*	X			X		
Angiogram		X				
BUN / Creatinine Concentration	X		X	X	X	X
Abdominal Ultrasound (Optional)			X	X	X	X

*Pre-Treatment CT obtained within 120 days of submission for screening, including chest, abdomen and pelvis. Abdomen and pelvis at follow-up visits.

4.2 Follow-up Visit Windows

Follow-up visits will be scheduled at appointed times after the date of treatment. The Sponsor recognizes that Subjects may not be able to return for follow-up visits on the exact date required. Thus, a period during which each visit is allowed, i.e., window, is provided below (Table 2). Follow-up visits should be scheduled within the ideal window when possible; however, any available data collected in the analysis windows will be summarized as occurring within the given window. Data collected outside the ideal window, but within the analysis window will not be considered a protocol deviation. Subjects discharged from the hospital before the one month follow-up window (0-22 days post-treatment) are required to return for a one month follow-up visit including radiologic imaging. Subjects discharged during the one month ideal follow-up visit window (23-44 days post-treatment) are not required to return for a one month visit or imaging, provided the required CTA is obtained as part of the discharge assessment.

DICOM imaging collected during the follow-up phase of the study will be provided to the Sponsor for archival purposes. DICOM CT scans will be provided to the Core Lab for analysis.

Table 2: Schedule of Follow-up Visits and Time Periods

Follow-up Visit	Ideal Window (days)	Analysis Window (days)
Procedure	0	0
Discharge*	Before hospital discharge	N / A
Post-Procedure	Not required	1-14
1 Month	23-44	15-59
6 Months	150-210	60-242
12 Months	275-455	243-546
24 Months	640-820	547-911
36 Months	1005-1185	912-1275
48 Months	1370-1550	1276-1640
60 Months	1735-1915	1641-2006

*Follow-up visit is categorized as “Discharge” through initial hospitalization, regardless of length.

4.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will advise the Sponsor regarding the continuing safety of study Subjects. The AAA 13-02 DSMB will be comprised of an interdisciplinary team of members with pertinent expertise in vascular and / or cardiothoracic surgery who are not directly involved in the conduct of the study. The members will be compensated for their involvement in the DSMB, including reimbursement for reasonable travel expenses to attend meetings.

This committee will operate under pre-specified procedures and timelines as outlined in the DSMB Charter. The DSMB will be responsible for conducting periodic reviews of aggregate data on a prescribed basis. The frequency of data review and other roles and responsibilities of the DSMB will be specified in the DSMB Charter.

Based on the safety data, the DSMB will make recommendations to the Sponsor. Recommendations may include study termination, study continuation with or without major or minor modifications, temporary suspension of enrollment and / or study intervention until some uncertainty is resolved. All final decisions regarding study modifications rest with the Sponsor.

4.4 Clinical Event Committee

A Clinical Events Committee (CEC), consisting of the six participating Investigators will ensure consistent and accurate AE and death reporting and classification. No study Investigators on the CEC will review events from their Institution. CEC will adjudicate selected safety AEs according to the definitions provided in Appendix A of the protocol.

This committee will operate under pre-specified procedures and timelines as outlined in the CEC Charter. Selected summaries of the safety events outlined in the protocol will be prepared based on the CEC adjudication.

The CEC will be responsible for review and adjudication of key AEs in the AAA 13-02 study. Specifically:

- The CEC will review reported AEs which potentially meet the definition of a primary safety endpoint event. The CEC will adjudicate the AEs provided to them against the definitions in Appendix A of the protocol and make a final determination of the AE against the available endpoints. Primary safety endpoint events to be adjudicated include death, stroke, myocardial infarction, bowel ischemia, paraplegia, respiratory failure, and renal failure.
- The CEC will review reported AEs which potentially meet the definition of device integrity endpoints through one year of follow-up including loss of functional patency in any branch component due to thrombus or mechanical failure of the branch components, loss of functional patency in the main body component(s) due to thrombus or mechanical failure of the main body component(s), separation of the branch components from the main body component(s), or separation of the main body component(s) from the accessory components (DBC and / or contralateral limb components).
- The CEC will adjudicate events they receive as serious or non-serious for primary safety, device integrity, and any other events that are forwarded for adjudication.
- Additional events may be chosen to be adjudicated by CEC members if deemed necessary by the study team.

The members may be compensated for their involvement in the CEC, including reimbursement for reasonable travel expenses to attend meetings.

4.5 Core Laboratory

Analysis of pre-treatment and follow-up radiologic images will be conducted by an independent Core Lab. At a minimum, the assessment will include:

- patency of components
- presence of endoleaks and vessel rupture
- presence of wire fractures and component separation
- maximum aortic diameter

The Core Lab may use the study imaging to further refine measurement techniques that could be applied in future studies.

5.0 Statistical Analyses

5.1 Analysis Populations

All enrolled Subjects will be included in reported data.

5.2 Timing of Analyses

Analysis of the study results will be ongoing throughout enrollment. Regular case review by the DSMB and Sponsor will occur throughout enrollment. A final endpoint analysis will occur

when enrollment is complete and available Subjects have completed 12-month follow-up assessment. Serial analyses of long-term results will occur during the follow-up period. No adjustment to overall alpha level will be made since this is an exploratory study designed to evaluate basic feasibility.

5.3 Statistical Analysis of Endpoints

Due to the exploratory nature of this study, statistical analysis will be limited to summary statistics, including frequency counts for categorical variables, and measures of dispersion for continuous variables. No inferential analysis will be performed.

5.4 Additional Analyses

5.4.1 Device Events

Device events will be determined by MedDRA term as outlined in the AE Review Charter and will be presented in a summary table by follow-up period and total.

5.4.2 Core Laboratory

An independent Core Laboratory (Core Lab) will provide review of imaging data collected during the study at pre-treatment and follow-up.

Summaries of qualitative Core Lab imaging findings (endoleak, wire fracture, component separation, patency, and rupture) will be provided at each analysis window. The denominator for each category will be the number of subjects with a CT imaging assessment in the given window which is read by the Core Lab.

5.4.3 Site Poolability

Site data will be pooled based on clinical comparability, i.e., the study sites followed a common protocol, the study was monitored to assure compliance with the protocol and applicable government regulations, and the data collection and handling procedures were the same at all study sites.

5.5 Adverse Events

Adverse Events (AEs) are defined as any untoward medical occurrences, unintended disease or injury or any untoward clinical signs in a subject whether or not related to the investigational medical device. All AEs will be recorded on the appropriate eCRF and documented in the permanent medical record. The Investigator at each Site is ultimately responsible for reporting all AEs to the Sponsor.

5.5.1 Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device or procedure. Relationships include:

Study Device-related

If the functioning or characteristics of the device caused or contributed significantly to the adverse event, the adverse event would be suspected as primarily related to the Device.

Study Procedure-related

If the procedure caused or significantly contributed to the adverse event, the adverse event would be suspected as primarily related to the procedure.

Unrelated

If an adverse event cannot be attributed to the device or procedure, it will be reported as “Unrelated”.

Unknown relationship

If the relationship of the adverse event to the device or procedure cannot be determined, it will be coded as “Unknown”.

5.5.2 Adverse Event Classification

Each AE will be assessed by the Investigator to determine if it is serious or non-serious, as defined below. Note: Emergency room visits and 23-hour observations may not constitute hospitalization.

A Serious Adverse Event (SAE) 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.

Any event that does not meet the definition of serious will be classified as non-serious.

5.5.3 Adverse Event Reporting and Coding

Adverse Events will be reported on the appropriate eCRF and documented in the subject’s permanent medical record. The Investigator at each Site is ultimately responsible for reporting AEs to the Sponsor. The Investigator shall supply the Sponsor and IRB with any additional requested information.

The following information on each reported Adverse Event will be collected:

- Adverse Event Name
- Adverse Event Onset Date
- Relationship
- Classification [Serious / Non-Serious]
- Treatment
- Outcome
- Resolution Date

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

Adverse Event submission guidelines:

- Adverse Event reporting begins once the patient is enrolled in the study. All AEs should be reported from enrollment 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.
- Adverse Events 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 left as “Ongoing” on the AE CRF.
- Clinical sequelae present at baseline should be recorded on the Medical History Case Report Form. If the clinical sequelae increase in severity or frequency from baseline then it should be reported as an AE.

5.5.4 Subject Death

Death is not an adverse event but instead an outcome of an AE. Any ongoing or unresolved AEs at the time of death will be indicated as ongoing/continuing on the case report form. Attempts should be made by the investigative Site to obtain death certificates, autopsy reports and device explants when at all possible.

6.0 Interim Analyses and Safety Monitoring Analyses

Safety data will be periodically reviewed by a Data Safety and Monitoring Board (DSMB). A comprehensive summary of all reported adverse events will be reviewed. Specific adverse events of clinical interest in this patient population will include, but are not limited to stroke, myocardial infarction, bowel ischemia, paraplegia, respiratory failure, renal failure, or those attributable to loss of patency in the main body or branch components.

7.0 Analysis Specifications

7.1 Verification Level for Statistical Output

All necessary analysis datasets as well as tables referenced herein will be verified at Level I. All listings and figures referenced herein will be verified at Level II. Verification levels are explained in MD111325 Clinical Affairs Biostatistics Analysis Specification and Programming Procedure.