



Statistical Analysis Plan

GORE® Carotid Stent Clinical Study for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy

The Gore SCAFFOLD Clinical Study

Protocol #: GCS 10-08

SAP Version: 10-JUN-2014

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of GCS 10-08. It summarizes the analyses that will be performed to determine the safety and effectiveness of the GORE® Carotid Stent for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy. This SAP outlines tables, figures, and listings that are included in reports for the GCS 10-08 clinical study.

2.0 Study Design

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of the GORE® Carotid Stent for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy.

2.1.2 Secondary Objective(s)

No secondary objectives were specified for this study.

2.2 Study Treatment Arms

2.2.1 Test Arm and Test Device

The test arm will consist of consecutively enrolled, prospectively treated and followed subjects who satisfy all of the inclusion and none of the exclusion criteria. Test subjects will be treated with the GORE® Carotid Stent, hereafter referred to as the *test device*.

2.2.2 Control Arm

This is a single-arm clinical study with no concurrently enrolled control subjects for comparison. The comparator for the primary hypothesis test will consist of a performance goal developed from published carotid endarterectomy outcomes in a high-risk population.

2.3 Enrollment

A patient is considered an enrolled subject in the study when the test device enters the patient's vasculature, also referred to as "test device attempted." Enrollment of the subject is indicated in the study data system by a response of Yes to Question 18 of the Procedure CRF, "Was a GORE® Carotid Stent introduced into the subject's anatomy?"

2.4 Design Summary

This is a prospective, multicenter, single-arm, clinical study comparing outcomes with the GORE® Carotid Stent (test device) to a performance goal.

A maximum of 50 investigative sites in the U.S., Europe, and Japan will participate in this study. Three hundred twelve (312) subjects will be enrolled in this study with a limit of 40 subjects enrolled at any single site. The anticipated accrual rate is approximately 15-20 subjects per month for a total accrual period of approximately 18-24 months.



Patients may be enrolled into the clinical study provided all inclusion and no exclusion criteria are met. Subjects will be evaluated through hospital discharge and return for follow-up visits at 30 days, 6 months, and 1, 2, and 3 years post-procedure.

The total study duration from start-up to close-out is expected to be 60 months. A full analysis of all relevant data will be submitted to the FDA and PMDA for PMA and Shonin approval upon completion of the primary endpoint analysis.

2.5 Study Endpoints

2.5.1 Primary Endpoint

The primary study endpoint is a composite of Major Adverse Events (MAE) defined as death, any stroke, or myocardial infarction (MI) through 30 days post-index procedure, and ipsilateral stroke between 31 days and 1 year (365 days). All primary endpoint events will be adjudicated and determined by the study Clinical Events Committee (CEC).

2.5.2 Secondary Endpoints

Stent Technical Success: Successful deployment of the test device.

EPD (Embolic Protection Device) Technical Success: Technical success for the GORE® Embolic Filter is defined as: EPD delivered, placed, and retrieved without requiring assisting interventional methods.

Procedure Success: Stent Technical Success, <30% residual angiographic stenosis by visual assessment post-procedure in the target lesion and no in-hospital (pre-discharge) Major Adverse Event.

30-Day Major Adverse Events: Composite of death, any stroke, or myocardial infarction through 30 days post-index procedure.

In-stent Restenosis: Measured as percent stenosis at follow-up evaluation within the stented lesion or within 5 mm proximal or distal to the stent. Additionally will assess percent of subjects with stenosis $\geq 50\%$ by ultrasound and $\geq 80\%$ by angiographic evaluation.

Target Lesion Revascularization (TLR): any clinically driven revascularization procedure of the original treatment site, including angioplasty, stenting, endarterectomy, or thrombolysis, performed to open or increase the luminal diameter inside or within 5 mm of the previously treated lesion.

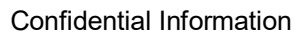
2.6 Statistical Hypotheses

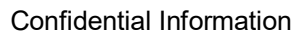
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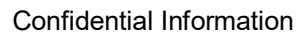
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$$H_0: P_a + P_c \geq \text{[REDACTED]}$$

$$H_1: P_a + P_c < \text{[REDACTED]}$$







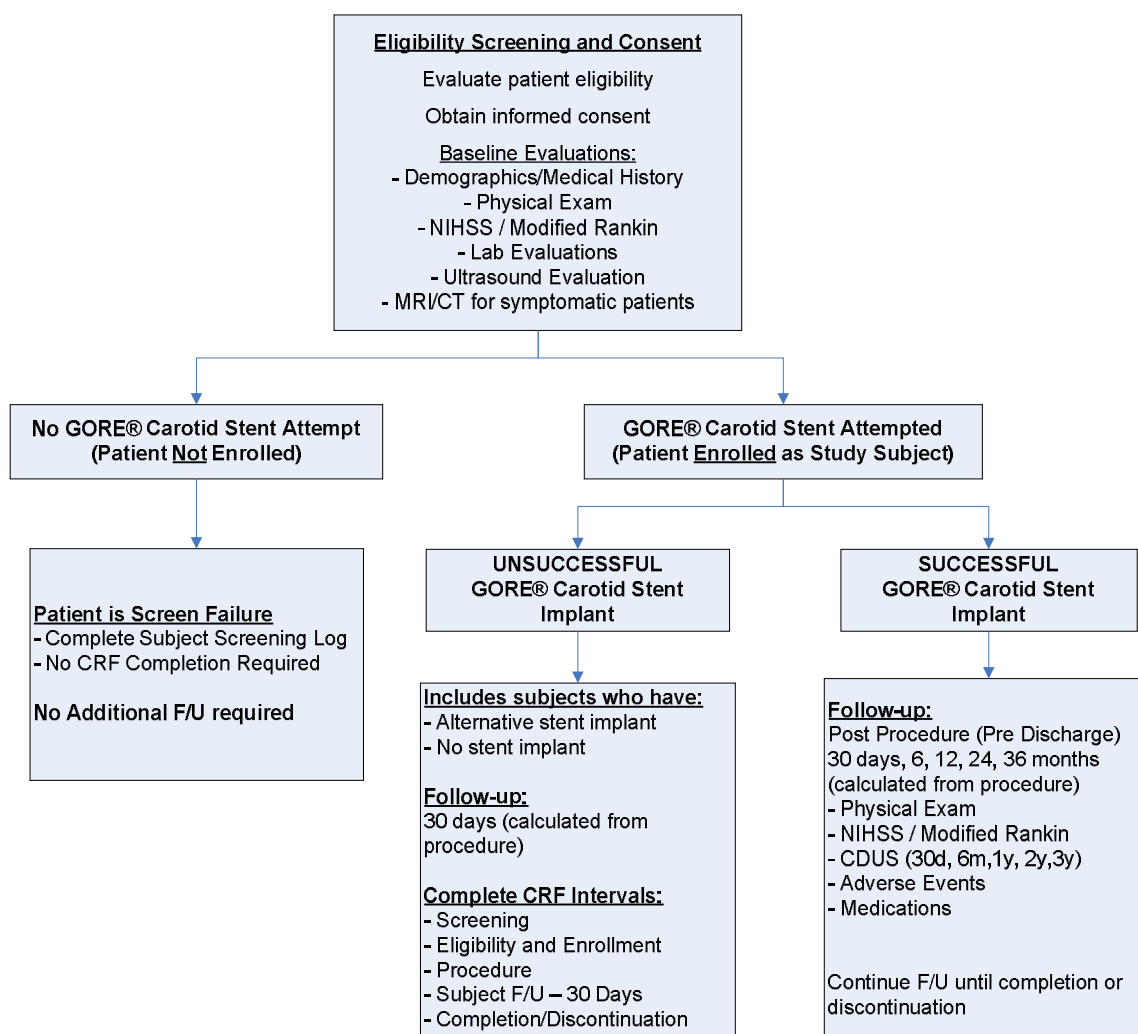
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3.0 Study Data Collection

3.1 *Study Data Collection Intervals*

Figure 2 below shows expected evaluations depending on a subject's enrollment status and technical outcome.

Figure 2. Study Procedures and Evaluation Schema


3.2 Study Interval Windows

Subjects with successful test device implant will return for follow-up at 30 days, 6 months, 1, 2 and 3 years. Subjects considered Technical Failures (test device attempted but not implanted) are only required to complete a 30-day follow-up and will have then completed the study. All intervals are calculated from the index procedure. The 6-Month visit target is 180 days. The yearly visits are calculated on a calendar year from index procedure.

30 Days	6 Months	1 Year	2 Years	3 Years
30±7 days	180±14 days	365±30 days	730±45 days	1,095±45 days

3.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will oversee conduct of the study. The DSMB will review accumulating study safety data on a regular basis and will advise the Sponsor regarding the continuing safety of study subjects as well as the continuing validity and scientific merit of the study. The DSMB will be comprised of an interdisciplinary team of at least 3 members (2 voting physicians, and one voting statistician) with pertinent expertise in carotid stenting 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 prespecified procedures as outlined in the DSMB Charter in accordance with the FDA's Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees. 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 review, the DSMB will make recommendations to the Sponsor. Recommendations may include 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.

3.4 Clinical Events Committee

An independent Clinical Events Committee (CEC) will review potential primary endpoint events and adjudicate events based on endpoint definitions in the study protocol. The CEC will be comprised of an interdisciplinary team with pertinent knowledge in carotid stenting or the cardiovascular and/or nervous system who are not directly involved in the conduct of the study. The members will be compensated for their involvement in the CEC, including reimbursement for reasonable travel expenses to attend meetings.

This committee will operate under prespecified procedures as outlined in the CEC Charter. The adjudication process will be initiated after a potential primary endpoint event is reported by the site.

3.5 Site Enrollment Restrictions

A maximum of 50 investigative sites in the U.S., Europe, and Japan will participate in this study. Three hundred twelve (312) subjects will be enrolled in this study with a limit of 40 subjects enrolled at any single site. The anticipated accrual rate is approximately 15-20 subjects per month for a total accrual period of approximately 18-24 months.

3.6 Core Labs

This study will utilize a carotid duplex ultrasound core lab and an angiographic core lab. Specific administrative information on these core labs can be found in the study protocol.

4.0 Statistical Analyses

4.1 Analysis Sets

The primary endpoint will be analyzed both on an intent-to-treat basis and on a per-protocol basis. The primary analysis set for testing of the primary endpoint is the per-protocol analysis set.

4.1.1 Intent-To-Treat (ITT) Analysis Set

The ITT analysis set is defined as all enrolled subjects (test device attempted) with adequate informed consent, regardless of whether or not the test device was implanted. Because technical failures (test device attempted but not implanted) are followed only to 30 days, this set will be used in the analysis of safety endpoints (major, serious, and

nonserious adverse events) to 30 days and secondary endpoints evaluated at procedure, discharge, and 30 days.

4.1.2 Per-Protocol Analysis Set (Primary Analysis Set)

For per-protocol analysis, only subjects who had the test device implanted in the target vessel and had no major protocol deviations will be included in the analysis. Major protocol deviations are defined as protocol deviations with a level of seriousness such that inclusion of the subject(s) would unacceptably bias the primary endpoint analysis. An example of a major protocol deviation might be failure to satisfy eligibility criteria to a degree where the subject does not fit the underlying scientific model for the treatment.

The per-protocol set will be used for the primary analyses of the primary endpoint. Ideally this analysis set will consist of all subjects from the ITT set with technical success (test device implanted).

4.2 Timing of Analyses

4.2.1 Primary Endpoint Analysis

The primary endpoint analysis will occur when enrollment has been completed and primary endpoint status has been determined for all enrolled and implanted subjects (generally after the one-year follow-up has been completed).

4.2.2 Staged Analysis

In accordance with the IDE approval letter from FDA dated December 13, 2012, the Gore SCAFFOLD Clinical Study was initially limited to enrollment of 100 subjects, with the following interim analysis requirement:

"Your IDE application has been approved as a staged study. You may request approval to expand enrollment in your study when you have submitted an IDE supplement which provides the 6-month results from the first 50 patients enrolled."

Thus, when the 6-month follow-up evaluation is completed (or final 6-month follow-up status determined) for the first 50 subjects enrolled, the data for these 50 subjects will be analyzed and results presented for safety and efficacy endpoints measured at procedure, 30 days and 6 months.

4.3 Primary Endpoint

The primary endpoint of 1-year MAE will be calculated as a subject-based binomial proportion. The numerator will be the count of subjects who experience death, any stroke, or MI through 30 days post-index procedure, or ipsilateral stroke through one year (365 days) post-index procedure. The denominator will be the count of subjects free of MAE and with clinical follow-up of at least 335 days post-index procedure, plus the count of subjects in the numerator. Only MAE adjudicated by the CEC will be used in this analysis. Acceptable clinical follow-up includes the Subject Evaluation CRF, duplex ultrasound, modified Rankin scale, and NIHSS.

A one-sided 95.1% upper confidence bound will be calculated (using the standard error based on H_0) and compared to the prespecified performance goal. If this bound is less than the performance goal, then the primary endpoint is met and the test device will have demonstrated acceptable performance. The P value for the corresponding one-sided normal

approximation to the binomial test will be reported. The primary hypothesis test will use $\alpha=0.049$ to ensure an overall Type-1 error rate ≤ 0.05 .

4.4 Secondary Endpoints

Secondary endpoints (subject-based unless otherwise specified) will be descriptive only; no formal statistical hypotheses will be tested. Secondary endpoints will be summarized at the specified time points using the descriptive statistics described above. No claims of statistical significance will be made based on secondary endpoint results. *P* values from these tests will not be reported in labeling, but may be used for scientific presentations and/or manuscripts.

Stent Technical Success: Successful deployment of the test device. It will be calculated as a subject-based binomial proportion. The numerator will be the count of subjects who experience successful deployment of the test device at the index procedure (based on the Procedure CRF). The denominator will be the count of subjects in whom implantation of the test device was attempted (based on the Procedure CRF).

EPD (Embolic Protection Device) Technical Success: EPD Technical success is defined as: GORE® Embolic Filter delivered, placed, and retrieved without requiring assisting interventional methods. It will be calculated as a subject-based binomial proportion. The numerator will be the count of subjects who experience successful use of the EPD during deployment of the test device at the index procedure (based on the Procedure CRF). The denominator will be the count of subjects in whom implantation of the test device was attempted (based on the Procedure CRF).

Procedure Success: Stent Technical Success, <30% residual angiographic stenosis by visual assessment post-procedure in the target lesion, and no in-hospital (pre-discharge) Major Adverse Event. It will be calculated as a subject-based binomial proportion. The numerator will be the count of subjects who experience Stent Technical Success and <30.0% "Post intervention lesion % residual stenosis" (from the Procedure CRF) and are free of any CEC-adjudicated in-hospital MAE. The denominator will be the count of subjects in whom implantation of the test device was attempted (based on the Procedure CRF).

30-Day Major Adverse Events: Composite of death, any stroke, or myocardial infarction through 30 days post-index procedure. It will be calculated as a subject-based binomial proportion. The numerator will be the count of subjects who experience CEC-adjudicated MAE through 30 days post-index procedure. The denominator will be the count of subjects free of MAE through 30 days post-index procedure and with clinical follow-up of at least 23 days post-index procedure, plus the count of subjects in the numerator.

In-stent Restenosis: Measured as percent stenosis at follow-up evaluation within the stented lesion or within 5 mm proximal or distal to the stent. Additionally will assess percent of subjects with stenosis $\geq 50\%$ by ultrasound and $\geq 80\%$ by angiographic evaluation.

The text above is taken verbatim from the clinical protocol. There are three separate endpoint measures implied by this description, defined below:

In-stent Percent Diameter Stenosis: calculated as a subject-based categorical frequency distribution of "In Stent Stenosis Category" as reported on the Carotid Artery Duplex Scan CRF among subjects with a valid, nonmissing value for this item.

The stenosis categories are the following:

- Patent
- 50-79%
- >70%
- 80-99%
- Occluded

In-stent Restenosis By Ultrasound: calculated as a subject-based binomial proportion. The numerator will be the count of subjects with stenosis $\geq 50\%$ by ultrasound (indicated as any valid, nonmissing stenosis category other than "Patent") as reported on the Carotid Artery Duplex Scan CRF. The denominator will be the count of subjects with a valid, nonmissing value for this item.

In-stent Restenosis By Angiography: calculated as a subject-based binomial proportion. Restenosis failures will be indicated by an angiography core lab-adjudicated stenosis of $\geq 80\%$ as reported on the Angio Core Lab Adjudication CRF. Not all subjects will have a follow-up angiography performed, only those whose ultrasound-determined stenosis and/or clinical symptoms provokes an angiography by the investigator. The denominator will be the count of subjects with a valid, nonmissing value for ultrasound-determined stenosis.

Target Lesion Revascularization (TLR): any clinically-driven revascularization procedure of the original treatment site, including angioplasty, stenting, endarterectomy, or thrombolysis, performed to open or increase the luminal diameter inside or within 5 mm of the previously treated lesion. This will be calculated using Kaplan-Meier (K-M) survival analysis. Events will be subjects who experience TLR as reported on the Reintervention CRF. Censored observations will be subjects free of TLR. K-M estimates corresponding to the study follow-up intervals will be reported, as well as a graph of the entire survival distribution.

4.5 Adverse Events

All site-reported AEs will be MedDRA coded and grouped by MedDRA System/Organ Class (SOC) and by MedDRA Preferred Term within SOC. AEs will also be grouped by seriousness (SAE vs. nonserious AE), primary relationship (stent, EPD, procedure, medication, disease, not related, and unknown) and timing of onset (procedure, pre- and post-discharge). AEs will be summarized as rates given by subject-based binomial proportions. The numerator will be the count of subjects who experienced one or more episodes of the AE of interest in the time period of interest. The denominator will be the count of subjects free of the AE of interest through the time period of interest and with sufficient clinical follow-up for the time period of interest, plus the count of subjects in the numerator. Unless otherwise specified for a particular endpoint measure, all enrolled subjects in the analysis set of interest will be considered evaluable and will contribute to the denominator.

4.6 Comparison of Baseline Data

A comparison of baseline data is not applicable in this single-arm study with a performance goal comparator.

Subject demographics, clinical history, risk factors, and preprocedure lesion characteristics will be summarized for all subjects using descriptive statistics for continuous variables

(mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample).

4.7 Subgroup Analysis of Primary Endpoint

In addition to the overall analysis, the primary endpoint will also be analyzed controlling for the following baseline covariates: age, sex, and race/ethnicity.

4.8 Subgroup Analysis of Key Secondary Endpoints

No subgroup analyses are planned for any of the secondary endpoints.

4.9 Poolability of Investigative Sites

The data from all investigative sites will be pooled based on the assumption of clinical comparability: the sites used a common protocol; the sponsor adequately monitored the study to assure protocol compliance; and the data gathering and validation mechanisms were the same across all study sites.

Analyses to justify pooling will include the following:

- The primary endpoint will be presented by site.
- An assessment of the poolability of the sites using a 2-by-(number of sites) contingency table of MAE outcome versus site. Fisher's Exact Test will be used to assess homogeneity. Sites with fewer than five subjects will be combined based on geographic region.
- If the sites are found to be significantly heterogeneous with respect to the primary endpoint, additional analyses will be conducted to assess differences between sites in baseline and procedural variables that might explain differences in primary outcome.

Although the protocol specifies the study will enroll subjects from investigative sites in the U.S., Europe and Japan, at the time of writing this analysis plan it appears unlikely that any sites will be initiated and subjects enrolled outside of the U.S. As such, it appears unlikely that a justification of poolability of global regions will be necessary. In the event that sites are initiated and subjects enrolled outside of the U.S., then appropriate analyses stratified by global region will be performed.

4.10 Additional Analyses

Additional subgroup analyses may be performed based on variables identified to be significant predictors ($p\text{-value} < 0.05$) in multivariate analyses.

Sensitivity analyses of the primary endpoint will be conducted and will include, at a minimum, a worst-case analysis (nonevaluable subjects considered failures) and, if necessary, a tipping point analysis (threshold of successes vs. failures at which the primary test conclusion changes).

5.0 Interim Analyses

No interim analyses to test the study hypotheses are planned.

6.0 Analysis Specifications

6.1 *SAS Analysis Dataset Specifications*

A specifications document is created for each analysis data set and contains, at a minimum:

- Dataset name
- Variable name
- Format
- Label
- Study database input field(s) and/or calculation logic

6.2 *Statistical Output Specifications*

A specifications document, or “spec,” is created for each statistical output (Table, Listing, or Figure) and contains, at a minimum:

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

6.3 *Verification Level for Statistical Output*

Verification levels for statistical output are defined per MD111325. The minimum required verification levels for various statistical output are as follows:

- All Analysis Datasets – Level 1
- All Tables – Level 1
- All Figures – Level 2
- All Listings – Level 2
- *Ad Hoc* or *Post Hoc* analyses – Level 3

7.0 References

MD111325 – Clinical Affairs Biostatistics Analysis Specifications and Programming Procedure



8.0 Revision History

Log of Changes Made to the Statistical Analysis Plan

Version Date	Initiated By	Summary of Change
02-Aug-2013	Bryan Randall	Initial Version
09-Jun-2014	Bryan Randall	<ol style="list-style-type: none">1. Added Section 2.3 Enrollment2. Clarified definitions of analysis sets in Section 4.13. Added Section 4.2.2 Staged Analysis4. Clarified in-stent restenosis definitions in Section 4.45. Removed Section 7.0 Datasets, Tables, Figures, and Listings