Statistical Analysis Plan

GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with *Patent Foramen Ovale* (PFO)

The Gore REDUCE Clinical Study

Protocol #: HLX 06-03

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the REDUCE clinical trial. It details the analyses that will be performed to accomplish these objectives. This SAP defines variables and identifies methods and algorithms used to populate the tables, figures, and listings that are included in reports for this study.

2.0 Study Design

2.1 Objectives

2.1.1 Primary Objectives

The primary objective of this study is to demonstrate that antiplatelet medical management plus PFO closure with the GORE® HELEX® Septal Occluder / GORE® CARDIOFORM Septal Occluder (study device) reduces the risk of a recurrent stroke or imaging-confirmed TIA compared to antiplatelet medical management alone in patients with a patent foramen ovale (PFO) and history of cryptogenic stroke or imaging-confirmed TIA.

A co-primary objective is to demonstrate that medical management plus closure with the study device reduces the risk of new brain infarct compared to medical management alone.

2.1.2 Secondary Objectives

Evaluate the safety and efficacy of the study device for the transcatheter closure of PFO.

2.2 Design Summary

The Gore REDUCE Clinical Study is a prospective, randomized, multinational, multicenter evaluation comparing antiplatelet medical management without PFO closure (control arm) to PFO closure with the study device plus antiplatelet medical management (test arm) for the reduction of recurrent stroke or imaging-confirmed TIA or new brain infarct in subjects with a PFO and history of cryptogenic stroke or imaging-confirmed TIA.

A total of 664 eligible subjects will be randomized to either the test or control arm using a 2:1 randomization scheme. A maximum of 80 investigational sites in the United States, Canada, and Europe will participate in the study with no per-site subject limit. The anticipated accrual rate is approximately 10 subjects per month for a total accrual period of approximately 60-66 months.

Randomized subjects will be followed for up to five (5) years. For the control arm, follow-up intervals will be calculated from the date of randomization. For the test arm, follow-up intervals will be calculated from the date of the transcatheter closure procedure. All subjects will receive follow-up evaluations at 1, 6, 12, 18, 24, 36, 48, and 60 months. Test arm subjects will receive an additional follow-up evaluation at early post-procedure (within 4 to 72 hours following the transcatheter closure procedure).

2.3 *Randomization and Enrollment*

A patient is considered an enrolled subject in the study upon randomization to one of the two treatment arms, Test or Control. Randomization will be weighted 2:1 in favor of the test arm. The randomization plan does not stratify by site or any other baseline variables.

2.4 *Study Treatment Arms*

2.4.1 Test Arm and Test Device

The test arm will consist of enrolled subjects who were determined by the randomization process to receive the test treatment regimen, which consists of prompt antiplatelet medical therapy and PFO closure with the test device within 90 days of randomization. At the start of enrollment in December 2008, the test device was the GORE® HELEX® Septal Occluder; with Protocol Amendment 2, dated May 15, 2012, the test device was changed to the GORE® CARDIOFORM Septal Occluder.

2.4.2 Control Arm

The control arm will consist of enrolled subjects who were determined by the randomization process to receive the control treatment regimen, which consists of prompt antiplatelet medical therapy alone, with no closure of the PFO.

2.5 *Study Endpoints*

2.5.1 Primary Endpoints

Co-primary Endpoint 1 is freedom from a recurrent stroke or imaging-confirmed TIA through at least 24 months post-randomization. For this study, a **recurrent stroke or imaging-confirmed TIA event** is defined as the first occurrence, post-randomization, of one of the following:

- Clinical finding of ischemic stroke that may be associated with MRI evidence of a new relevant brain infarction. For this study, an ischemic stroke is defined as a neurological deficit, presumed due to ischemia, persisting longer than 24 hours or until death.
- Clinical finding of TIA that also has MRI evidence of a new relevant brain infarction. For this study, a TIA is defined as a transient neurological deficit, presumed due to ischemia, persisting less than 24 hours.

Co-primary Endpoint 1 will be calculated as the time from randomization to the first recurrent event. Subjects free from a recurrent event will be censored at the date of last known contact.

All deaths and suspected recurrent stroke/TIA events will be reviewed and adjudicated by a Clinical Events Committee (CEC). In the event of subject death, all possible efforts will be made to obtain relevant records from the hospital or the subject's primary care physician, including a death certificate or autopsy report, to determine the cause of death.

Co-primary Endpoint 2 is the incidence of subjects with new brain infarct or stroke from screening through 24 months or last follow-up visit, whichever occurs first, hereinafter referred to as **brain infarct.** A responder is defined as any subject with at least one new T2 hyperintense MRI lesion with diameter ≥ 3 mm from screening or clinical findings of ischemic stroke, through 24 months or last follow-up visit, whichever occurs first. It will be calculated as a subject-based binomial proportion.

2.5.2 Secondary Endpoints

Safety Endpoints will include the proportion of subjects who experience adverse events (AEs) that are determined to be related to device, procedure, and/or antiplatelet medical management. This will include specific adverse events and groups of adverse events such as all-cause adverse events, device-related events, procedure-related events, antiplatelet medical therapy-related events, and any serious adverse events.

The safety endpoints may also be analyzed using time-to-event methods to estimate the percentage of subjects free from the event at time points of interest, such as 30 days and 24 months post-randomization (or post-procedure for the test arm).

Efficacy Endpoints will evaluate the success of the device in achieving PFO closure in subjects randomized to the test arm. PFO closure success will be measured by assessing the degree of residual right-to-left shunt after device implant. Time points for the assessment of PFO closure include early post-procedure, 1 month, 12 months, and 24 months.

Additional Secondary Endpoints will include:

1. **Clinical Success** –
   a. Test Arm – defined as the composite of Device Success, PFO closure, and absence of a recurrent stroke or imaging-confirmed TIA at 24 months post-procedure
   b. Control Arm – defined as the freedom from a recurrent stroke or imaging-confirmed TIA at 24 months post-randomization
2. **Overall Survival** – defined as time from randomization to death from any cause or last known contact
3. **Time to any stroke/TIA** – defined as time from randomization to first occurrence of stroke or TIA
4. **Device Success** – defined as the proportion of device arm subjects with successful implant and retention of the device after procedure (test arm only)

2.6 Statistical Hypotheses

This study is designed to test the null hypothesis that the hazard of a recurrent stroke or imaging-confirmed TIA in subjects treated with percutaneous PFO closure plus antiplatelet medical management is equal to or higher than subjects treated with antiplatelet medical management alone. The alternative hypothesis is that the hazard of a recurrent stroke/imaging-confirmed TIA is lower in subjects treated with percutaneous PFO closure plus antiplatelet medical management compared to antiplatelet medical management alone. In statistical terms:

$$\mathbb{H}_0: HR_{T/C}(t) \geq 1.0 \; for \; all \; t$$
$$\mathbb{H}_1: HR_{T/C}(t) < 1.0 \; for \; all \; t$$

where $HR_{T/C}$ is the hazard ratio comparing the test (T) arm to the control (C) arm.

In addition, this study will test the null hypothesis that the incidence of brain infarct at 24 months in subjects treated with percutaneous PFO closure plus antiplatelet medical management is equal to or higher than subjects treated with antiplatelet medical management alone. The alternative hypothesis is that the brain infarct incidence is lower in subjects treated with percutaneous PFO

closure plus antiplatelet medical management compared to antiplatelet medical management alone. In statistical terms:

H_0: $P_C - P_T \leq 0$
H_1: $P_C - P_T > 0$

where:

P_C = true proportion of subjects with incident brain infarct in the control group
P_T = true proportion of subjects with incident brain infarct in the test group

2.7 Sample Size Determination

2.7.1 Sample Size Assumptions

Based on literature available at the study's initiation (see Section 1.0 of the study protocol), the proportion of PFO patients free from a recurrent stroke or imaging-confirmed TIA at 24 months after initial, cryptogenic stroke or imaging-confirmed TIA is assumed to be approximately 92%, with a range of 86% to 94%. For the purposes of determining sample size for adequate power, a 55% reduction in the hazard of a recurrent stroke or imaging-confirmed TIA is considered a clinically relevant benefit.

At the time this study was designed, Co-primary Endpoint 2 was considered a secondary endpoint and was not relevant to the sample size assumptions.

2.7.2 Randomization and Enrollment

Subjects will be randomized in a 2:1 allocation ratio with the greater proportion of subjects randomized to the test arm. Enrollment of 120 to 140 subjects per year is anticipated, for a total enrollment period of 60-66 months (5 to 5.5 years).

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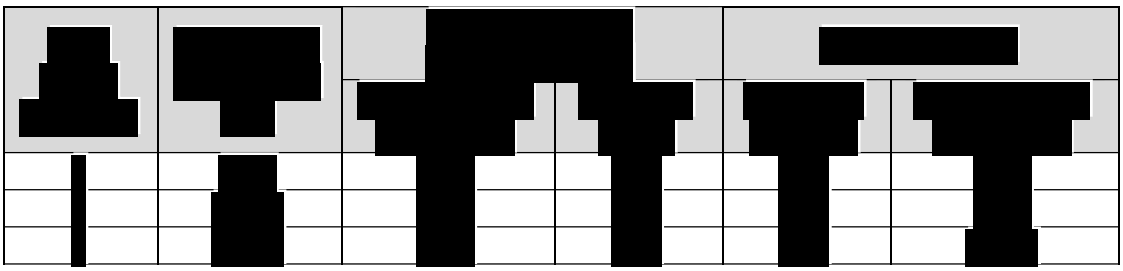


3.0 Study Data Collection

3.1 Study Data Collection Intervals

Refer to Section 5, Data Collection And Evaluation, in the protocol.

3.2 Study Interval Windows

For Test Arm subjects, all follow-up intervals are calculated from the day of the PFO closure procedure.

Schedule of Test Arm Subject Follow-up and Visit Windows

Follow-up Visit Interval	Follow-up Visit Interval Window
Early Post-procedure	Typically 4-72 hours post-PFO closure procedure, but must be completed prior to leaving the hospital, out-patient facility, or surgical center
1 month	1 month (30 days) ± 2 weeks (14 days)
6 months	6 months (182 days) ± 1 month (30 days)
12 months	12 months (365 days) ± 2 months (60 days)
18 months	18 months (547 days) ± 2 months (60 days)
24 months	24 months (730 days) ± 2 months (60 days)
Year 3	36 months (1,095 days) ± 2 months (60 days)
Year 4	48 months (1,460 days) ± 2 months (60 days)
Year 5	60 months (1,825 days) ± 4 months (120 days)

For Control Arm subjects, all follow-up intervals are calculated from the day of randomization.

Schedule of Control Arm Subject Follow-up and Visit Windows

Follow-up Visit Interval	Follow-up Visit Interval Window
1 month	1 month (30 days) ± 2 weeks (14 days)
6 months	6 months (182 days) ± 1 month (30 days)
12 months	12 months (365 days) ± 2 months (60 days)
18 months	18 months (547 days) ± 2 months (60 days)
24 months	24 months (730 days) ± 2 months (60 days)
Year 3	36 months (1,095 days) ± 2 months (60 days)
Year 4	48 months (1,460 days) ± 2 months (60 days)
Year 5	60 months (1,825 days) ± 4 months (120 days)

3.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be comprised of an interdisciplinary team of five individuals, four physicians and a biostatistician, who are not directly involved in the conduct of the study.

The team shall include, at minimum, one stroke neurologist, one interventional cardiologist, and a biostatistician to assist with formulation of stopping rules and direction of interim analyses.

The members may be compensated for their participation in the DSMB, including reimbursement for reasonable travel expenses to attend meetings. Members will not have any business or financial affiliation with the study sponsor, the core laboratories, or the study investigators.

The DSMB is responsible for conducting periodic reviews of aggregate data on a prescribed schedule. Based on the safety data, the DSMB will make recommendations to the Sponsor. Recommendations may include modifying the study, stopping the study, or continuing the study. All final decisions regarding study modifications or study continuation, however, will rest with the Sponsor.

3.4 Clinical Events Committee

The independent Clinical Events Committee (CEC) will be comprised of at least three physicians who are not participating in the study and do not have any conflicts of interest with the study Sponsor. The CEC will include representatives from at least three of the following specialties/disciplines:

- stroke neurology
- interventional cardiology
- echocardiography
- neuroradiology

Input from other disciplines will be solicited, if required. The members may be compensated for their involvement in the CEC including reimbursement for reasonable travel expenses to attend meetings.

The committee will be responsible for:

- Review of definitions of clinical endpoints in the study in conjunction with the Sponsor.
- Review and adjudication of adverse events that have the potential to be study endpoint events, including death, stroke, and TIA; AND
- Subsequent classification of these adverse events as related to the study device, procedure, or medications.

3.5 Site Enrollment Restrictions

There is no per-site subject enrollment limit specified for this study.

3.6 Core Labs

An independent MRI Core Laboratory will provide centralized assessment of study endpoints from protocol-required MRI and CT imagery. Three board-certified radiologists with specific neurological

imaging expertise will be responsible for the review of all MRI and CT images. The principal measures provided by this core lab are detection of new brain infarct from screening to 24 months for the brain infarct endpoint, and detection of brain infarct for the recurrent event endpoint, especially regarding confirmation of a TIA as a recurrent event. The core lab readers are blinded to treatment in their image assessments.

Similarly, an independent Echocardiography Core Laboratory will provide centralized assessment of study endpoints from protocol-required echocardiography imagery, principally to confirm the presence of PFO in all subjects and to assess PFO closure status at follow-up for test subjects. Three board-certified cardiologists with expertise in echocardiography will be responsible for the review of all echocardiograms.

Refer to Section 3.19, Imaging Analysis, in the protocol.

4.0 Statistical Analyses and Methods

4.1 Analysis Sets

The co-primary endpoints will be analyzed under several different analysis set definitions, as described below. The primary analysis set for testing of the co-primary endpoints is the intent-to-treat analysis set.

4.1.1 Intent-To-Treat (ITT) Analysis Set (Primary Analysis Set)

The ITT analysis set is defined as all enrolled subjects (randomized to treatment) and will be analyzed by treatment assigned at randomization, regardless of whether or not the correct treatment was administered.

4.1.2 Per-Protocol Analysis Set

For per-protocol analysis, only subjects who were randomized and treated according to protocol will be analyzed by treatment assigned at randomization. Specifically, subjects randomized to test who received antiplatelet medical therapy and PFO closure with the test device, and subjects randomized to control who received antiplatelet medical therapy and no PFO closure by any means, will be included in the analysis.

4.1.3 As-Treated Analysis Set

For as-treated analysis, subjects who were randomized and treated will be analyzed by treatment received, regardless of treatment assigned at randomization. Specifically, randomized subjects who received antiplatelet medical therapy and PFO closure by any means (test device, alternative device, surgery) will be analyzed in the “PFO Closure” group, and randomized subjects who received antiplatelet medical therapy and no PFO closure by any means will be analyzed in the “No PFO Closure” group.

4.2 Timing of Analyses

4.2.1 Primary Endpoint Analysis

The primary endpoint analysis will be performed when the last subject enrolled completes 24 months of follow-up.

4.2.2 Interim Analyses

The original protocol specified that, in addition to standard study monitoring, an interim analysis will be performed after approximately 50% of the total expected recurrent stroke or imaging-confirmed TIA events have occurred. This milestone event had not occurred as of the completion of full enrollment in February 2015. Under the plan described herein, the original interim analysis plan no longer serves its purpose and is rescinded.

4.3 Primary Endpoints

4.3.1 Freedom From Recurrent Event

Co-primary Endpoint 1, freedom from a recurrent event, will be compared between treatment groups using an unadjusted log-rank test and presented using Kaplan-Meier methods. All follow-up data through 5 years will be included on subjects continuing follow-up past the 24-month evaluation. As part of a simultaneous test with the brain infarct co-primary endpoint hypothesis (described in sections 4.3.2 and 4.5 below) a multiplicity-adjusted p-value for the hazard ratio test of 0.025 or less will be considered evidence to reject the freedom from recurrent event null hypothesis.

4.3.2 Brain Infarct

The analysis sample for Co-primary Endpoint 2, brain infarct, will consist of randomized subjects with valid MRI Core Lab data at screening and an appropriate follow-up, where follow-up will be at 24 months or immediately following a recurrent event (suspected stroke or TIA), whichever occurs first, as well as randomized subjects who experience a confirmed recurrent event through 24 months regardless of MRI data status. Responders are subjects who show one or more new infarction(s) on MRI since screening or experience a confirmed recurrent event. Nonresponders are subjects who do not show new infarction on MRI since screening and do not experience a confirmed recurrent event.

The primary analysis will be a two-sample comparison of the binomial proportion of subjects with brain infarct between the two treatment groups. Each binomial proportion will be calculated as the count of responders divided by the count of evaluable subjects (sum of the responder and nonresponder counts).

The hypothesis will be tested using a two-sample binomial proportions test:

$$z = \frac{p_C - p_T}{\sqrt{\frac{p_C(1-p_C)}{n_C} + \frac{p_T(1-p_T)}{n_T}}}$$

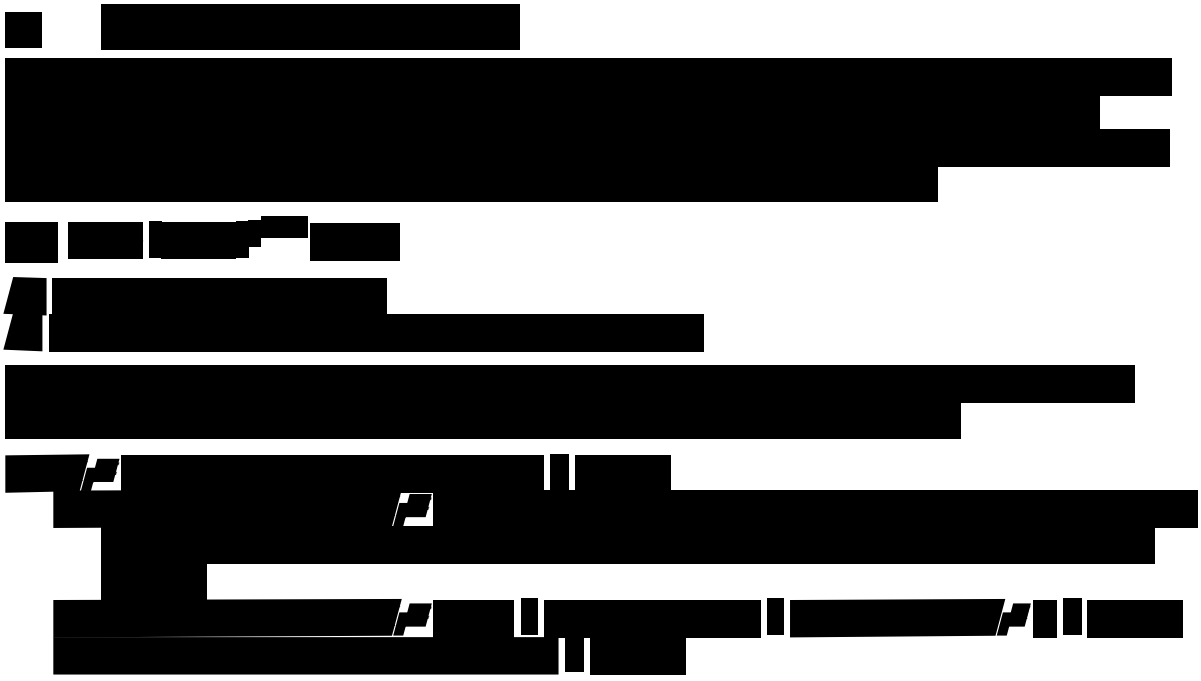
where:

p_C = observed brain infarct proportion in control group
n_C = number of evaluable subjects in control group
p_T = observed brain infarct proportion in test group
n_T = number of evaluable subjects in test group

The test statistic z is assumed to have a standard Normal distribution. The significance level for this test will be set at a 1-sided α = 0.025, but the p-value will be adjusted for multiplicity with the 1-sided α = 0.025 test performed simultaneously on the primary endpoint. Therefore, $p_C - p_T > 0$ and a multiplicity-adjusted p-value $\leq$ 0.025 will result in rejection of the null hypothesis in favor of the alternative hypothesis and a conclusion that the test treatment reduces the rate of brain infarct compared to the control treatment. The 1-sided multiplicity-adjusted p-value and unadjusted 2-sided 95% confidence interval for the difference in proportions will be reported.

4.4 Secondary Endpoints

The secondary endpoint analysis will be performed in conjunction with the primary endpoint analysis. Statistical methods for testing multiple endpoints will be utilized in the comparison of secondary endpoints across test and control to preserve the overall Type I error rate.



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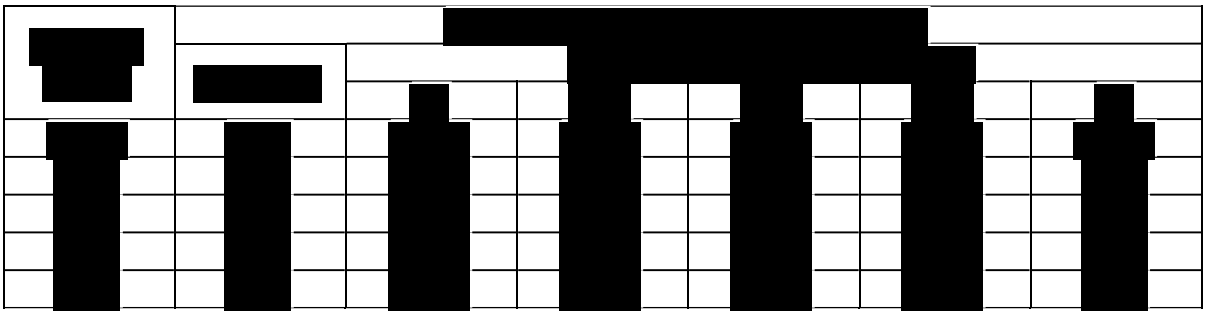

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Based on the final analysis of correlation between the two endpoints and the unadjusted p-values obtained from the two test statistics, the appropriate adjusted p-values will be compared to the overall 1-sided $\alpha = 0.025$ for the experiment.

4.6 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 (device, procedure, antiplatelet medication, unrelated, and unknown) and timing of onset (procedure, pre- and postdischarge). 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.

4.7 Comparison of Baseline Data

Subject demographics, clinical history, risk factors, and screening PFO 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). These measures will be compared between the test group and the control group using test methods appropriate for the measures, for example, two-sample t- or Wilcoxon rank-sum tests for continuous measures and chi-square or Fisher's exact tests for discrete measures.

4.8 Subgroup Analysis of Primary Endpoints

In addition to the overall analysis, the two co-primary endpoints will also each be analyzed controlling for region, defined as enrolled at a site within the United States (US) or enrolled at a site outside of the United States (OUS).

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: Kaplan-Meier estimates of freedom from recurrent event will be presented for the two treatment groups.
- An assessment of the poolability of the sites using a Cox regression model of recurrent event outcome with coefficient terms for treatment group (test, control), site, and treatment group-by-site interaction. Statistical significance of the interaction term will be used to make inferences on site homogeneity. Sites with fewer than five subjects will be combined based on geographic region (US versus OUS).
- 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.

Similar analyses to justify pooling for the brain infarct endpoint will be performed using a logistic regression model.

4.10 Additional Analyses

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

Sensitivity analyses of the recurrent event and brain infarct co-primary endpoints will be conducted and will include, at a minimum, a “worst-case” analysis (subjects who withdraw or are lost to follow-up considered recurrent events in the test group and censored in the control group), a “best-case” analysis (subjects who withdraw or are lost to follow-up considered censored in the test group and recurrent events in the control group), and, if necessary, a tipping point analysis (threshold of successes vs. failures between the treatment groups at which the primary test conclusion changes).

4.10.1 Evaluation of Septal Occluder Device Poolability

It is expected that shortly after approximately one-third of the subjects have been enrolled, the new study device (GORE® CARDIOFORM Septal Occluder) will become available and will be used as the device of choice within the test arm of the study. As a regulatory requirement, an assessment of poolability will be conducted for the two study device subgroups in the test arm. The statistical plan for this assessment will consist of two stages: baseline homogeneity and primary outcome comparability.

For baseline homogeneity, the two test device subgroups will be compared on the following six baseline demographic and predictor covariates: age, gender, qualifying cerebrovascular event, balloon-sized PFO diameter, PFO tunnel length, and presence of atrial septal aneurysm. These subgroup comparisons will use the two-sample t-test, chi-square test, or Fisher's Exact test, depending on the distribution of the covariate.

For primary outcome comparability, covariate-by-device interactions will be assessed using Cox proportional hazards regression models where main effects for device and the covariate and the covariate-by-device interaction term will be regressed on the 24-month freedom from recurrent stroke or imaging-confirmed TIA primary endpoint; this will be performed individually for each of the six baseline covariates. Statistically significant interactions will be assessed graphically for the nature of the interaction (quantitative vs. qualitative). Qualitative interactions (difference in direction of device effect across levels of covariate) will suggest differences between the device subgroups, leading to analyses performed separately for each device subgroup. A similar approach will be used for brain infarct comparability, but using a logistic regression model for this binary endpoint.

Finally, device subgroup and any baseline covariates deemed to be different between device subgroups will be included as main effects in a Cox regression model on the primary endpoint. If the device subgroup term is statistically significant and the observed hazard reduction (test vs. control) for either of the device subgroups is less than the hypothesized 55%, then the device subgroups will not be considered outcome comparable, leading to analyses performed separately for each device subgroup. Again, a similar approach will be used for the binary brain infarct endpoint, but using a logistic regression model instead of a Cox regression model.

A significance level of α=0.15 will be used for these poolability tests, without correction for multiplicity. Since this evaluation plan calls for a minimum of 13 significance tests per endpoint, the overall Type-I error rate per endpoint for these analyses may exceed $1 - (1 - 0.15)^{13} = 0.88$.

4.11 Interim Analyses

No interim analyses involving formal statistical testing of the study hypotheses are planned.

5.0 Analysis Specifications

5.1 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

5.2 Statistical Output Specifications

A specifications document 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 output 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

5.3 Verification Level for Statistical Output

Verification levels for statistical output are defined per MD111325. The minimum required verification levels for statistical output in this study 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

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7.0 Revision History

Log of Changes Made to the Statistical Analysis Plan

Version Date	Initiated By	Summary of Change
15-JAN-2016	Bryan Randall	Initial Version (Revision #1)