Statistical Analysis Plan

GORE® CARDIOFORM ASD Occluder Clinical Study: A study to evaluate safety and efficacy in the treatment of transcatheter closure of *ostium secundum* atrial septal defects (ASDs)

The Gore ASSURED Clinical Study

Protocol #: ASD 15-04

SAP Version: Revision #1, 27-FEB-2017

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses planned to address the objectives of the ASSURED 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 Primary Objective

The primary objective of this study is to evaluate the safety and efficacy of the GORE® CARDIOFORM ASD Occluder in the percutaneous closure of *ostium secundum* atrial septal defects (ASDs).

2.2 Design Summary

The Gore ASSURED Clinical Study is a prospective, multicenter, single-arm clinical study comparing outcomes for the GORE® CARDIOFORM ASD Occluder to performance goals derived from clinical investigation outcomes for devices indicated for ASD closure.

This clinical investigation will enroll up to 460 subjects (not including 2 training cases per site) from a protocol-specified maximum of 22[1] clinical investigational sites (referred to as "sites" in the remainder of this document) in the United States. Enrollment will occur in three phases: Pivotal (125 subjects, in addition to 2 training cases per site); Continued Access (up to 335 subjects); and Post-Approval (if required). Each phase will enroll sequentially.

All enrolled subjects with technical success will be followed through the 36-month follow-up; subjects with technical failure will be followed only through the 30-day follow-up. The analysis in support of pre-market approval submission will occur when the 125 pivotal (non-training) subjects have completed 6-month follow-up evaluations.

2.3 Randomization and Enrollment

This is a single-arm clinical study with no concurrently enrolled control subjects for comparison, and thus randomization is not applicable.

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 1 of the ENRL (Enrollment) CRF, *Was the study device introduced into the anatomy of the subject?*

[1] Although the current version of the study protocol (MD151471 Revision 2) states a maximum of 30 participating sites, approval for 22 sites was granted by FDA in IDE Supplement G160218/S001 dated January 3, 2017.

2.4 Study Treatment Arms

2.4.1 Test Arm and Test Device

The test arm will consist of consecutively enrolled, prospectively treated and followed subjects who were screened to meet the study eligibility criteria. Test subjects will be treated with the study (test) device: the GORE® CARDIOFORM ASD Occluder.

2.4.2 Control Arm

This is a single-arm clinical study with no concurrently enrolled control subjects for comparison. The comparators for the primary hypothesis tests will consist of performance goals derived from clinical study outcomes for devices indicated for ASD closure.

2.5 Study Endpoints

2.5.1 Primary Endpoints

Co-Primary Endpoint 1: **6-Month Closure Success** is defined as a clinical residual defect status of occluded or clinically insignificant as determined by the Echo Core Lab at the 6-month evaluation among subjects with technical success.

Co-Primary Endpoint 2: **Composite Clinical Success** is evaluated at 6 months after index procedure among subjects with attempted study device closure and is defined as satisfying all of the following criteria:

1. Technical Success: Successful deployment and retention (at conclusion of index procedure) of a GORE® CARDIOFORM ASD Occluder
2. Safety Success:
   - Freedom from any Serious Adverse Event (SAE) related to the device or procedure, as adjudicated by the Independent Data Review Board (IDRB) through 30 days post-procedure
   - Freedom from device events (post-procedure embolization, device removal, or other device reintervention) from completion of the implant procedure through 6 months (180 days) post-procedure
3. Closure Success: A clinical residual defect status of occluded or clinically insignificant as determined by the Echo Core Lab at the 6-month evaluation.

2.5.2 Secondary Endpoints

Technical Success: Successful deployment and retention of the study device at the conclusion of the index procedure

Procedure Success: Technical success and measured residual defect status of occluded, small, or moderate of the target ASD at conclusion of the index procedure

Long-term Closure Success: Closure success evaluated at 12 months and 36 months

Long-term Composite Clinical Success: Composite clinical success evaluated at 12 months and 36 months

Safety Outcomes: The proportion of subjects experiencing one or more SAEs within 30 days post-index procedure, and the proportion of subjects experiencing a device event (embolization; device removal; reintervention after completion of index procedure) through 6 months, 12 months, and 36 months post-index procedure

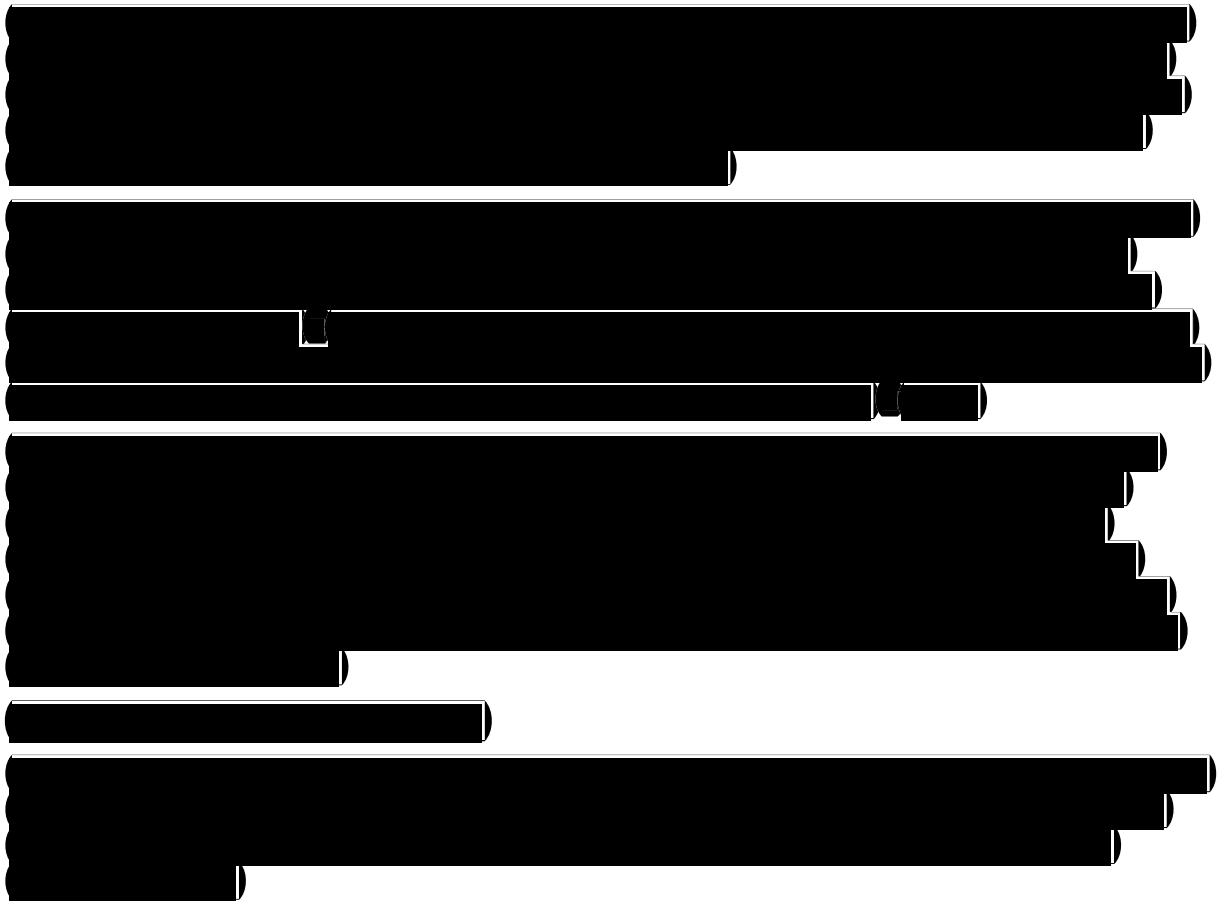
Clinically Significant New Arrhythmia: In subjects without prior history of arrhythmia, any new arrhythmia (documented on ECG) requiring hospitalization, initiation of new long-term medical therapy (persisting > 45 days), or any post-index procedure cardioversion or intervention (pacemaker, ablation, etc.)

2.6 Statistical Hypotheses

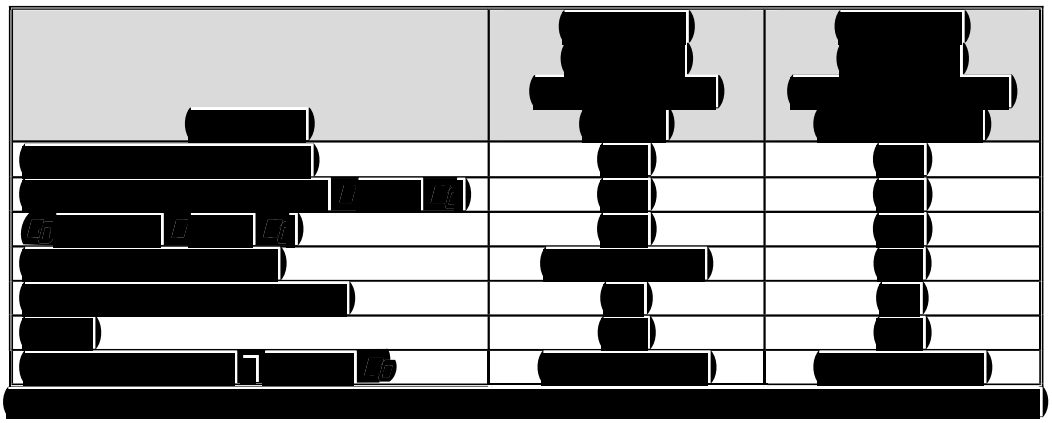
2.7 Sample Size Determination

2.7.1 [redacted]

[redacted]



2.7.2 [redacted]



3.0 Study Data Collection

3.1 Study Data Collection Intervals

Refer to Section 5, Study Procedures and Evaluations, in the study protocol (MD151471).

3.2 Study Interval Windows

Subjects with successful study device implant will return for follow-up visits at 30 days, and at 6, 12, and 36 months. For the 24-month assessment, subjects will be contacted by telephone. Subjects considered Technical Failures (study device attempted but not implanted) are only required to complete a 30-day follow-up telephone assessment and will then be discontinued from the study. All intervals are calculated from the index procedure (day 0). The visit windows are calculated as the target day plus or minus the appropriate number of calendar days. The 6-month visit target is 180 days. The yearly visits are calculated on a 365-day year from index procedure.

30 Days	6 Months	12 Months (1 Year)	24 Months (2 Years)	36 Months (3 Years)
30 ± 14 days	180 ± 14 days	365 ± 60 days	730 ± 60 days	1095 ± 60 days

[3] Hintze, J. (2013). PASS 12. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com

3.3 Independent Data Review Board (IDRB)

Excerpt from section 9.7 of the study protocol:

During the course of the study, the IDRB will serve as both a Data and Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC). As the DSMB, the IDRB will review aggregate safety data for the course of the study to monitor the incidence of SAEs and other safety trends that could warrant modification or termination of the study. As the CEC, the IDRB will adjudicate all site-reported adverse events through 30 days post-procedure for seriousness and relatedness of potential primary endpoint events. In addition, the IDRB will review and adjudicate all site-reported AEs related to arrhythmia for the course of the study. The IDRB Charter will outline the responsibilities and operating procedures of the Board.

3.4 Site Enrollment Restrictions

A maximum of 22[4] investigative sites in the United States will participate in this study. One hundred twenty-five (125) non-training subjects will be enrolled in the Pivotal Phase of this study, with a limit of 10 non-training subjects enrolled at any single site during the Pivotal Phase. The first 2 subjects enrolled at each site will be considered training cases that do not apply to the above restrictions.

If approval is obtained to resume enrollment in the Continued Access Phase, up to 335 additional subjects may be enrolled. No individual site enrollment restrictions will apply to the Continued Access Phase.

3.5 Core Lab

All protocol-required echocardiographic and fluoroscopic imaging will be uploaded to the study imaging vendor's secure web portal. The core lab will access images via the secure web portal and perform evaluations on the 30-day, 6-, 12-, and 36-month echocardiographic images. Results of core lab evaluations will be recorded in the study database.

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.

4.1.1 Primary Analysis Set

There is no single primary analysis set for this clinical investigation, because the two co-primary endpoints each require different analysis sets, as described below.

[4] Although the current version of the study protocol (MD151471 Revision 2) states a maximum of 30 participating sites, approval for 22 sites was granted by FDA in IDE Supplement G160218/S001 dated January 3, 2017.

4.1.2 All Enrolled Subjects Analysis Set

This analysis set is defined as all subjects with a study device implant attempt, regardless of whether the study device was successfully implanted. The 6-month clinical success co-primary endpoint will be analyzed using this set, as will technical success, procedure success, and 30-day safety. However, because technical failures (study device attempted but not implanted) are followed only to 30 days, this set will not be used for the analysis of the 6-month closure success co-primary endpoint, nor any other postprocedure measures or outcomes.

4.1.3 Technical Success Analysis Set

This analysis set is defined as all subjects with a successful study device implant, (i.e. technical success). The 6-month closure success co-primary endpoint will be analyzed using this set, as will all other postprocedure measures or outcomes except technical success, procedure success, and all assessments of clinical success.

4.1.4 Per-Protocol Analysis Set

For per-protocol analysis, only subjects who had no major protocol deviations (PDs) will be included in the analyses. Major PDs are defined as PDs with a level of seriousness such that inclusion of the subject(s) would unacceptably bias analyses of the primary endpoints. An example of a major PD might be failure to satisfy eligibility criteria to a degree where the subject does not fit the underlying scientific model for the treatment. Per-protocol criteria may be applied to both the all enrolled subjects and the technical success analysis sets.

Protocol deviations that may be considered major and lead to exclusion of a subject from the per-protocol analysis set include: inclusion/exclusion criteria (eligibility) deviations; failure to obtain informed consent; and retention of more than one study device.

If necessary, per-protocol analysis sets will be used for additional analyses of the primary and secondary endpoints.

4.2 Timing of Analyses

4.2.1 Primary Endpoint Analysis

The primary endpoints analysis will be performed and submitted to FDA as a Pre-Market Approval (PMA) after 6-month follow-up is complete on the Pivotal Phase cohort.

4.2.2 Interim Analyses

An interim analysis of 30-day safety data on the Pivotal Phase cohort will be performed and submitted to FDA after 30-day follow-up is complete on all Pivotal Phase subjects. The purpose of this analysis and submission is to obtain approval to begin enrollment in the Continued Access Phase of the study. No formal statistical testing of study hypotheses is planned for this analysis.

4.3 *Primary Endpoints*

4.3.1 Test Method

The co-primary endpoints are both subject-based binomial proportions. For Co-Primary Endpoint 1, 6-Month Closure Success, exact binomial testing at the one-sided 5% significance level will be performed against the performance goal (null hypothesis proportion). If the observed proportion is greater than the performance goal and the statistical test p-value is ≤ 0.05, then the null hypothesis will be rejected in favor of the alternative hypothesis of acceptable performance. In addition, the 95% one-sided Clopper-Pearson confidence interval lower bound will be reported. Depending on the outcome of this test, Co-Primary Endpoint 2, Composite Clinical Success, will be tested by the same method.

4.3.2 Test Hierarchy for Multiplicity Control

The overall Type I error rate of 5% will be controlled for multiplicity by the following hierarchical testing structure:

1. Test $H_0^{Closure}$ at $\alpha = 0.05$.
2. If testing fails to reject $H_0^{Closure}$, then testing stops and $H_0^{Clinical}$ is as well not rejected.
3. If testing rejects $H_0^{Closure}$, then test $H_0^{Clinical}$ at $\alpha = 0.05$.

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. Any p-values from these tests will not be reported in labeling, but may be used for scientific presentations and manuscripts.

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 (device, procedure, study medication, and unrelated) 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.

4.6 *Baseline Characteristics*

Subject demographics, clinical history, risk factors, and pre-procedure defect characteristics will be summarized 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 Endpoints

The primary endpoints will also be analyzed controlling for the following baseline covariates: age; sex; race and ethnicity.

4.8 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:

- Each co-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 the primary outcome versus site. Fisher's Exact Test will be used to assess homogeneity. Sites with fewer than five subjects will be combined into one or more virtual sites based on geographic region, with the number of virtual sites dependent on the number of subjects represented by small sites (fewer than five subjects) and the geographic distribution of such sites. The maximum number of subjects in a combined, virtual site for this poolability analysis will be limited to 15 subjects.
- If the sites are found to be significantly heterogeneous with respect to the outcome (p-value ≤ 0.10), additional analyses will be conducted to assess differences between sites in baseline and procedural variables that might explain differences in the primary outcome.

4.9 Additional Analyses

4.9.1 Wire Frame Fracture

In order to assess possible harm to subjects due to wire frame fracture, an additional analysis involving co-primary outcomes as well as device-related adverse events will be conducted by stratifying subjects with and without frame fracture. To preserve the temporal relationship, only those events that had an onset date on or following the possible timing of frame fracture will be counted in the frame fracture subgroup.

4.9.2 Sensitivity Analyses

Sensitivity analyses of the clinical closure and clinical success 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 are considered failures), a "best-case" analysis (subjects who withdraw or are lost to follow-up are considered successes), and, if necessary, a tipping point analysis (threshold of imputed successes vs. failures at which the primary test conclusion changes).

4.9.3 Multivariable Modeling

Additional subgroup analyses may be performed based on variables identified to be significant predictors (p-value ≤ 0.05) in multivariate analyses. These subgroup analyses will be exploratory; no statistical inferences will be made.

5.0 Interim Analyses

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

6.0 Analysis Specifications

A specifications document is created for each analysis data set prior to programming.

Similarly, a specifications document is created for each statistical output (Table, Listing, or Figure) prior to programming.

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

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

[redacted]