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 Number: ASD 15-04

Amendment 3: 19 December 2018
Amendment 2: 28 February 2018
Amendment 1: 05 October 2017

Original Protocol: 15 November 2016

W. L. Gore & Associates, Inc.
Medical Products Division
4250 West Kiltie Lane
Flagstaff, AZ  86005

Telephone:  800-437-8181
Facsimile:  928-864-4957
**PROTOCOL SUMMARY**

<table>
<thead>
<tr>
<th>Study Title</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Number</td>
<td>ASD 15-04</td>
</tr>
<tr>
<td>Original Protocol</td>
<td>MD151471</td>
</tr>
<tr>
<td>IDE or PMA Number</td>
<td>G160218</td>
</tr>
<tr>
<td>Sponsor</td>
<td>W. L. Gore &amp; Associates, Inc. Medical Products Division 4250 West Kiltie Lane Flagstaff, AZ  86005 Telephone: 800-437-8181 Facsimile: 928-864-4957</td>
</tr>
<tr>
<td>Study Design</td>
<td>Prospective, multicenter, single-arm comparison to performance goals derived from clinical study outcomes for devices indicated for ASD closure</td>
</tr>
<tr>
<td>Study Objective</td>
<td>Evaluate the safety and efficacy of the GORE® CARDIOFORM ASD Occluder in the percutaneous closure of ostium secundum atrial septal defects (ASDs)</td>
</tr>
</tbody>
</table>
| Study Endpoints | **Primary Endpoints**  
Co-Primary Endpoint 1: 6-Month Closure Success among subjects with Technical Success.  
Co-Primary Endpoint 2: 6-Month Composite Clinical Success among subjects with attempted study device closure and defined as satisfying all of the following criteria:  
   1. Technical Success  
   2. Safety Success  
   3. 6-Month Closure Success  
**Secondary Endpoints**  
• Technical Success  
• Procedure Success  
• Long-term Composite Clinical Success  
• Long-term Closure Success  
• Safety Outcomes (subject-based rates of adverse events by MedDRA classification and seriousness)  
• Clinically Significant New Arrhythmia |
| Subject Population | • No age limitations  
• Patients with ostium secundum ASD measuring 8-35 mm by stop-flow balloon sizing  
• Inter-atrial shunting with evidence of right heart volume overload, demonstrating the need for septal defect closure |
**Number of Subjects**
- Absence of concurrent cardiac conditions that could elevate morbidity/mortality beyond what is common for ASD

<table>
<thead>
<tr>
<th>Number of Subjects</th>
<th>Number of Sites</th>
<th>Coordination Principal Investigator</th>
</tr>
</thead>
</table>
| Training Cases: First 2 subjects per site | Up to 22 sites in the U.S. | Matthew Gillespie, MD  Division of Cardiology  The Children's Hospital of Philadelphia  Room 6NE42, Main Bldg  34th & Civic Center BLVD  Philadelphia, PA 19104  National Principal Investigator, Pediatric  
Robert Sommer, MD  Center for Interventional Vascular Therapy  Columbia University Medical Center  627 West 165th Street, 5th floor Room 512  New York, NY 10032  National Principal Investigator, Adult |
| Pivotal Phase: 125 subjects (non-training) | | |
| Continued Access Phase: up to 535 subjects (non-training) | | |
| Total Study Enrollment: Up to 704 subjects | | |

**Expected Time to Complete Enrollment**
- Pivotal Phase (PMA Submission):
  - Enrollment Completion: 12 months
  - Follow-up Time: 6 months
  - Total Pivotal Duration: 18 months
- Continued Access Phase:
  - Enrollment Completion: 18-24 months
  - Follow-up Time: 3 years on all subjects
  - Total Study Duration: 5-5.5 years

**Schedule of Events**
- Screening Assessments (within 6 months of procedure)
  - Physical exam
  - Electrocardiogram (ECG)
  - Echocardiogram (TTE or TEE)
- Pre-Study Procedure (within 90 days of procedure)
  - Echocardiogram (TTE)
- Study Procedure
  - Physical exam
  - Stop-flow balloon sizing of defect
  - Echocardiogram (TTE, TEE or ICE)
  - Fluoroscopy
- Pre-Discharge
  - Electrocardiogram (ECG)
  - Echocardiogram (TTE)
- Follow-up Assessments
<table>
<thead>
<tr>
<th>30 days and 6 months:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Physical exam</td>
</tr>
<tr>
<td>• ECG</td>
</tr>
<tr>
<td>• Echocardiogram (TTE)</td>
</tr>
<tr>
<td>• Fluoroscopy (6 months for all Subjects)</td>
</tr>
<tr>
<td>Long-term follow-up will be performed at 1, 2, and 3 years.</td>
</tr>
<tr>
<td>The 1- and 3-year follow-up visits will include:</td>
</tr>
<tr>
<td>• Physical exam</td>
</tr>
<tr>
<td>• ECG</td>
</tr>
<tr>
<td>• Echocardiogram (TTE)</td>
</tr>
<tr>
<td>The 2-year follow-up will be a telephone questionnaire.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography Core Lab, Independent Data Review Board (IDRB)</td>
</tr>
</tbody>
</table>
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ASD</td>
<td>Atrial Septal Defect</td>
</tr>
<tr>
<td>CDMS</td>
<td>Clinical Data Management System</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Echo</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>ePTFE</td>
<td>expanded polytetrafluoroethylene</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>Fr</td>
<td>French Catheter Scale</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ICE</td>
<td>Intracardiac Echocardiography</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>IDE</td>
<td>Investigational Device Exemption</td>
</tr>
<tr>
<td>IDR</td>
<td>Independent Data Reviewer</td>
</tr>
<tr>
<td>IDRB</td>
<td>Independent Data Review Board</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>O.D.</td>
<td>Outer diameter</td>
</tr>
<tr>
<td>PAS</td>
<td>Post-Approval Study</td>
</tr>
<tr>
<td>PD</td>
<td>Protocol Deviation</td>
</tr>
<tr>
<td>PMA</td>
<td>Pre-Market Approval</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>systemic blood flow (Qs) is proportional to the pulmonary blood flow (Qp); this ratio is used in the measurement of physiologic shunt</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal Echocardiography</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic Echocardiography</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
</tbody>
</table>
PROTOCOL SUMMARY

LIST OF ABBREVIATIONS

1. Introduction
   1.1. Disease
   1.2. Study Device Description
      1.2.1. The GORE® CARDIOFORM ASD Occluder
      1.2.2. The GORE® CARDIOFORM ASD Occluder delivery system

2. Study Objectives
   2.1. Primary Objective(s)

3. Study Design
   3.1. Study Design Schema
   3.2. Description of Study Design
   3.3. Study Endpoints
      3.3.1. Study Definitions
      3.3.2. Primary Endpoints

4. Study Population
   4.1. Description of Population
   4.2. Inclusion Criteria
   4.3. Exclusion Criteria

5. Study Procedures and Evaluations
   5.1. Study Procedures and Evaluation Schema
   5.2. Schedule of Events
   5.3. Informed Consent Process
   5.4. Screening / Pre-treatment
      5.4.1. Screening / Pre-treatment Evaluation
      5.4.2. Pre-Procedural TTE
      5.4.3. Screen Failure
   5.5. Enrollment
      5.5.1. Transcatheter Procedure
      5.5.2. Recommended Procedure Technique (Instructions for Use)
      5.5.3. Access Site Management
      5.5.4. Pre-Discharge
      5.5.5. Unsuccessful GORE® CARDIOFORM ASD Occluder Procedure
   5.6. Post-Procedural Care
   5.7. Post-Procedural Evaluations and Testing
   5.8. Interventions
   5.9. Follow-Up
   5.10. Subject Withdrawal from the Study
   5.11. Subject Lost to Follow-Up
   5.12. Subject Study Completion
   5.13. Explant Procedures

6. Study Administration
   6.1. Training
   6.2. Monitoring
      6.2.1. Periodic Site Monitoring
# Table of Contents

6.2.2 Clinical Monitor Reports ........................................................................ 16  
6.3. Clinical Investigative Site Initiation Visit ................................................ 16  
6.4. Device Accountability and Storage ............................................................. 16  
6.5. Core Lab ................................................................................................. 16  
6.6. Protocol Deviations .................................................................................. 16  
6.7. Protocol Amendments ............................................................................ 17  
6.8. Sponsor Representatives ......................................................................... 17  
6.9. Access to Source Data/Documents .............................................................. 17  
6.10. Study Records Retention ......................................................................... 17  
6.11. Publication Plan ...................................................................................... 18  

7. **Data Collection and Submission** ................................................................ 19  
7.1. Data Collection Methods ........................................................................... 19  
7.2. Data Clarification and Correction ............................................................... 19  
7.3. CRF Completion Schedule ......................................................................... 19  

8. **Risk Assessment** ...................................................................................... 19  
8.1. Potential Risks .......................................................................................... 19  
8.2. Minimization of Risks ............................................................................. 20  
8.3. Summary of Expected Benefits ................................................................ 21  

9. **Adverse Events and Safety Monitoring** .................................................... 21  
9.1. Anticipated Adverse Events ..................................................................... 21  
9.2. Adverse Event Relationship .................................................................... 21  
9.3. Adverse Event Seriousness Classification ................................................. 22  
9.4. Adverse Event Reporting and Coding ....................................................... 23  
9.5. Subject Death ........................................................................................ 23  
9.6. Unanticipated Adverse Device Effects ..................................................... 24  
9.7. Independent Data Review Board (IDRB) .................................................... 24  

10. **Statistical Analysis** .................................................................................. 24  
10.1. Study Hypotheses .................................................................................. 24  
10.2. Sample Size Assumptions ..................................................................... 25  
10.3. Sample Size Determination .................................................................. 27  
10.4. Data Analysis ......................................................................................... 27  
10.4.1 Timing of Analyses ............................................................................. 27  
10.4.2 Baseline Characteristics ..................................................................... 27  
10.4.3 Analysis Sets ...................................................................................... 28  
10.4.4 Pooling of Data .................................................................................. 29  
10.4.5 Statistical Analysis of Primary Endpoint(s) .......................................... 29  
10.4.6 Sensitivity Analyses ........................................................................... 29  
10.4.7 Statistical Analysis of Secondary Endpoint(s) ................................... 29  

11. **Ethical and Regulatory Considerations** .................................................... 30  
11.1. Statement of Compliance ....................................................................... 30  
11.2. Compliance Responsibilities .................................................................. 30  
11.3. Informed Consent .................................................................................. 31  
11.4. Independent Ethical Review ................................................................... 31  
11.5. Conflict of Interest ................................................................................ 31  
11.6. Confidentiality ...................................................................................... 31  
11.7. Emergency / Compassionate Use ........................................................... 32  
11.8. Study Discontinuation or Suspension ..................................................... 32
1. Introduction

1.1. Disease

Ostium secundum atrial septal defects (ASDs) present as a persistent communication between the atria and are a common congenital cardiac anomaly accounting for approximately 10% of all congenital heart disease. They are one of the most common congenital heart defects to present in adulthood. Untreated, ASDs produce right heart volume overload and progressive impairment over time, including reduced aerobic capacity, atrial dysrhythmias, congestive heart failure, pulmonary hypertension, and potential paradoxical embolism. In the United States (U.S.) alone it is estimated that approximately 10,000 new patients per year can be expected to have an ASD identified.

Historical Treatments

Successful surgical repair of ASD has been performed for 50 to 60 years with continued improvement in technique and outcomes. King and Mills reported the first transcatheter closure of ASD in 1976, but the delivery system was quite large and impractical, especially for younger patients. With time, improvements in design concepts and materials discoveries have led to improved results in transcatheter closure systems. Several devices are now available commercially for transcatheter ASD closure.

1.2. Study Device Description

The GORE® CARDIOFORM ASD Occluder is a permanently implanted occluder being tested for the indication of percutaneous, transcatheter closure of ostium secundum atrial septal defects (ASDs). The occluder system consists of an implantable occluder and a delivery system. The occluder is comprised of a platinum-filled nickel-titanium (Nitinol) wire frame covered with expanded polytetrafluoroethylene (ePTFE).

The investigational medical device is manufactured by W. L. Gore & Associates, Inc. (Gore) at 4250 W. Kiltie Lane, Flagstaff, Arizona 86005. More detailed device information can be found in the Instructions for Use (IFU) and Investigators Brochure (IB).

1.2.1.
2. **Study Objectives**

2.1. **Primary Objective(s)**

Evaluate the safety and efficacy of the GORE® CARDIOFORM ASD Occluder in the percutaneous closure of *ostium secundum* atrial septal defects (ASDs).
3. Study Design

3.1. Study Design Schema

```
<table>
<thead>
<tr>
<th>Phase</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal Phase</td>
<td>125</td>
</tr>
<tr>
<td>(125 subjects + 2 training cases per site)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continued Access Phase</td>
<td>up to 535</td>
</tr>
<tr>
<td>(up to 535 subjects)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Study Cohort</td>
<td>up to 704</td>
</tr>
</tbody>
</table>

Analysis #1 — To support Continued Access Phase:
125 enrolled subjects with 30-day follow-up

Analysis #2 — To support PMA submission:
125 enrolled subjects with 6-month follow-up

Analysis #3 — Final analysis:
All enrolled subjects with 36-month follow-up
```

3.2. Description of Study Design

This is a prospective, multicenter, single-arm clinical study comparing outcomes with 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 704 subjects (including 2 training cases per site) from a maximum of 22 clinical investigational sites (referred to as “sites” in the remainder of this document) in the U.S. Enrollment will occur in three phases — Pivotal (125 subjects, in addition to 2 training cases per site), Continued Access (up to 535 subjects), and Post-Approval (if required). Each phase will enroll sequentially (see Study Schema 3.1).

Only sites that enroll at least one subject (which includes the first training case) in the Pivotal Phase are eligible to enroll subjects in the Continued Access Phase.

- Training case subjects will be identified using Subject IDs referenced with numbers 101-199 within the study database
- Pivotal Phase subjects will be identified using Subject IDs referenced with numbers 201-299 within the study database
- Continued Access Phase subjects will be identified using Subject IDs referenced with numbers 301-399 within the study database

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 subjects have completed 6-month follow-up evaluations.

3.3. Study Endpoints

3.3.1. Study Definitions

Target ASD — Target ASD refers to:
- the ASD that is selected by the investigator for device closure via transcatheter means
- the ASD that is measured by stop-flow balloon sizing for inclusion in the study
Non Target ASD – Non Target ASD refers to:
- Any additional defects not identified and treated as target ASD by the investigator

Clinical Residual Defect Status – categories defined based on clinical characteristics at study follow-up intervals as determined by the Echocardiography (Echo) Core Lab:
1. Completely Occluded, defined as absence of detectable residual shunt using transthoracic echocardiographic (TTE) color flow doppler
2. Clinically Insignificant Residual Shunt, defined as the following:
   Residual shunt is hemodynamically insignificant based on all of the following characteristics:
   i. Improvement of ventricular septal motion, defined as reduction of paradoxical septal wall motion as compared to pre-procedural TTE
   ii. Decrease in right ventricular size as determined by comparison of corresponding pre-procedural TTE parasternal and apical images of the right ventricle pre- and post-device placement
3. Clinically Significant Residual Shunt, defined as any of the following:
   i. A residual left-to-right shunt or right heart volume overload which has not changed from the pre-procedure TTE that would likely require repeat intervention
   ii. Hemodynamically significant, defined as failure to meet criteria for hemodynamically insignificant detailed above

Measured Residual Defect Status – If present, residual defect size of the target ASD should be measured at post-implant, pre-discharge, and all subsequent follow-up evaluations. During the core lab analysis, the categories will be defined based on measured size of the target ASD residual shunt and compared to the guideline below:
- Occluded: absence of residual shunt
- Small: > 0 to ≤ 3 mm residual shunt
- Moderate: > 3 to ≤ 6 mm residual shunt
- Large: > 6 mm residual shunt

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

Enrolled Subject: A subject is considered enrolled into the clinical study when the study device is introduced into the anatomy of the subject.

3.3.2. 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.

3.3.3 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**: A calculation of the proportion of subjects experiencing one or more SAEs within 30 days post-index procedure or 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.).

4. **Study Population**

4.1 Description of Population

Subjects with an ostium secundum ASD having a stop-flow balloon diameter of 8-35 mm may be enrolled. Baseline variables are assessed by means of physical examination, ECG, and TTE or transesophageal echocardiography (TEE).

Subjects with additional cardiac conditions requiring surgery at the time of ASD closure or anticipated within three (3) years of enrollment are not permitted in the study due to possible confounding Adverse Events (AEs). Overall health, age, and other underlying conditions should be considered prior to patient enrollment.

The study has been designed with standard eligibility criteria to address any known or foreseeable factors that may compromise the outcome of the study or the interpretation of results. Only patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be enrolled.
This study includes individuals from potentially vulnerable populations such as children. A vulnerable individual is defined as one whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Participating sites must comply with IRB-specific requirements regarding protection of vulnerable populations.

4.2 Inclusion Criteria

All responses must be Yes to be eligible:
1. Patient has an ostium secundum ASD with evidence of left-to-right shunt and right ventricular volume overload.
2. Patient has a defect size 8-35 mm as measured directly by stop-flow balloon sizing.
3. Patient vasculature can accommodate the delivery system and procedural accessories.
4. Patient can accommodate TEE or intracardiac echocardiography (ICE) probe for implant procedure.
5. Patient is judged by the implanting physician to have adequate septal rims to retain the study device.
6. Patient (or legal guardian, if patient is a minor) will voluntarily sign a Patient Informed Consent Form (ICF) specific to the study. The Patient ICF must be reviewed and approved in a manner that complies with requirements of the hospital's Institutional Review Board (IRB).
7. Patient (and legal guardian, if patient is a minor) is physically and mentally willing to comply with all study follow-up requirements through 36 months, including routinely scheduled diagnostic testing and physical examinations.

4.3 Exclusion Criteria

All responses must be No to be eligible:
1. Patient has significant known pre-existing electrophysiologic or structural cardiovascular defect, or other comorbidities that could elevate morbidity or mortality beyond what is common for ASD or would require surgical treatment within three (3) years of device placement. Examples include, but are not limited to, large ventricular septal defect, hypoplastic left heart syndrome, coarctation, univentricular heart or tricuspid atresia, pulmonary hypertension, coronary artery disease, valvular or myocardial dysfunction, and other congenital heart disease requiring surgical repair.
2. Patient has systemic or inherited conditions that would significantly increase risk of major morbidity and mortality during the term of the study. Examples include endocarditis, cancer, degenerative neuromuscular disorder, cardiomyopathy, and any condition expected to result in significant deterioration of health within three (3) years of the index procedure.
3. Patient has anatomy where the size or position of the occluder would interfere with other intracardiac or intravascular structures, such as cardiac valves or pulmonary veins.
4. Patient has active endocarditis, other infections producing bacteremia, or has known sepsis within one month of planned implantation, or any other infection that cannot be treated successfully prior to device placement.
5. Patient has known intracardiac thrombi.
6. Patient has an uncontrolled arrhythmia with evidence of arrhythmia control failure within the past 90 days (e.g., supraventricular tachycardia while under rate control or atrial fibrillation while under rhythm control) or requires electrophysiology study or concomitant intervention with device placement.

7. Patient is awaiting a procedure that requires trans-septal left atrial access within 6 months of implant procedure.

8. Patient has a history of stroke resulting in a significant morbidity or disability.

9. Patient is pregnant or lactating at time of screening.

10. Patient has contraindication to antiplatelet and anticoagulant medications.

11. Patient has elevated pulmonary vascular resistance (PVR) which in the opinion of the implanting physician precludes safe defect closure.

12. Patient has multiple defects based on screening imaging and stop-flow balloon sizing that would require placement of more than one device.
5. **Study Procedures and Evaluations**

5.1. Study Procedures and Evaluation Schema

Please refer to section 5.2 and study protocol for complete schedule of events.
5.2 Schedule of Events

The table below presents the procedures and evaluations for each protocol interval.

<table>
<thead>
<tr>
<th>Procedure / Evaluation</th>
<th>Screening (within 180 days of index procedure)</th>
<th>Pre-procedure (within 90 days of index procedure)</th>
<th>Pre-discharge</th>
<th>Unsuccessful Implant (day 30 ±14 days)</th>
<th>30 Days (day 30 ±14 days)</th>
<th>6 Months (day 180 ±14 days)</th>
<th>12 Months (day 365 ±60 days)</th>
<th>24 Months (day 730 ±60 days)</th>
<th>36 Months (day 1095 ±60 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Evaluation and estimated defect size</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TTE, TEE or ICE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Informed Consent &amp; HIPAA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics and Medical History</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (if applicable)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTE/TEE/ICE/Fluoroscopy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECG</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Antiplatelet Therapy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Concomitant Medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Telephone Questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Assess Adverse Events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fluoroscopy (Enface and lateral views)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Fluoroscopy at pre-discharge is at Investigator discretion

5.3 Informed Consent Process

All patients must provide informed consent (or parent/guardian consent for minor patients) prior to any study-related procedures being performed. The case history (i.e., source documents or subject chart) for each subject shall document that such informed consent was obtained. The IRB-approved consent form will be signed and personally dated by the...
subject or legally authorized representative, and the person who conducted the informed consent discussion. The original signed ICF will be retained in the subject records. A copy of the informed consent document will be given to the subject for their records.

5.4. Screening / Pre-treatment

In all cases, the investigator maintains exclusive responsibility for the inclusion and exclusion of any potential study participant. All patients presenting for treatment of ASD are evaluated for study participation based on the inclusion/exclusion criteria provided in this protocol.

5.4.1. Screening / Pre-treatment Evaluation

When the investigator identifies a patient as a potential candidate for inclusion in the clinical investigation, the necessary medical history, physical exam, (including pregnancy test, if applicable), and inclusion/exclusion criteria are reviewed. If the patient meets the criteria for entry into the study, the Patient ICF is administered.

A screening evaluation is performed within six months (180 days) of anticipated procedure to identify initial suitability of defect closure. This pre-treatment patient evaluation will assess eligibility variables by means of physical examination, ECG, TTE or TEE, or other appropriate imaging. Patients with an estimated static defect size of > 35 mm should not be considered for study participation.

Patients with additional cardiac conditions anticipated to require surgery within three years of enrollment are not permitted in the study. In addition, no concurrent interventions should be performed during the occluder procedure.

5.4.2. Pre-Procedure TTE

Within 90 days of the planned procedure, a TTE must be completed in accordance with the Echo Core Lab Guidelines. These images will be used by the core lab as a comparator for follow-up TTE assessments.

5.4.3. Screen Failure

Patients who consent to participate in the clinical investigation, but in whom no study device implant or placement is attempted, will be considered screen failures and will not be enrolled in this clinical investigation (see Study Schema, Section 5.1). No post-procedure study follow-up or contact will be required for these patients. Screen failures will be recorded on the appropriate Case Report Form (CRF) in the Electronic Data Capture (EDC) system.

5.5. Enrollment

A subject is considered enrolled into the clinical investigation when the study device is introduced into the anatomy of the subject.

5.5.1. Transcatheter Procedure

Subjects will undergo placement of the GORE® CARDIOFORM ASD Occluder via a transcatheter procedure. During the transcatheter procedure either TEE, TTE, or ICE will be performed with general anesthesia or conscious sedation based on the institution’s or investigator’s general practice.
- Procedure time begins upon venous cannulation and procedure time ends upon removal of the final catheter.
- Procedure anesthesia time begins when the subject is intubated and ends when the subject is extubated.

At that time, under general anesthesia or conscious sedation and by utilizing TEE, TTE, ICE, or calibrated fluoroscopy, static sizing, and stop-flow balloon sizing of the defect is performed. Assessment of cardiac anatomy, static defect sizing of < 35 mm and stop-flow balloon sizing of defects ranging between 8 mm and 35 mm will determine final patient suitability and the appropriate device size for closure of the defect.

Data will be recorded to characterize the procedure.

5.5.2. Recommended Procedure Technique (Instructions for Use)

Detailed IFU for placement of the GORE® CARDIOFORM ASD Occluder may be found in the GORE® CARDIOFORM ASD Occluder package as well as in the Study Regulatory Binder.

The following recommendations should be considered when choosing the appropriate GORE® CARDIOFORM ASD Occluder:

**Sizing the Defect and Selecting the Proper Occluder Size**

1. Use echocardiography to measure the maximum septal length
2. Measure the septal defect using fluoroscopy or echocardiography; the stop-flow balloon technique is recommended, as described below:
   - Place a contrast-filled, compliant balloon across the defect and gently inflate until shunting through the defect has stopped.
   - Measure the diameter of the defect using either echocardiography or calibrated fluoroscopy.
3. Select the appropriate occluder size (Occluder Configuration) for the defect taking the following recommendations into consideration (Reference Table 1):
   - The stop-flow defect size should be no less than 8 mm and no greater than 35 mm.
   - An occluder that pulls through the defect after disc conformation may be too small and should be removed and replaced with a larger size.
   - To assure that there is adequate space to accommodate the discs within the atrial chambers, the selected occluder maximum nominal outer disc diameter should be less than 90% of the measured septal length.
   - The septal tissue margins surrounding the defect must be of sufficient size and integrity to prevent disc prolapse through the defect and occluder embolization
     - Removal of the occluder should be considered if:
       - The lock loop fails to capture the right eyelet
       - The occluder will not come to rest in a planar position opposing the septal tissue
       - The selected occluder allows excessive shunting
       - There is impingement on adjacent cardiac structures
Table 1: GORE® CARDIOFORM ASD Occluder Device Sizing

<table>
<thead>
<tr>
<th>Maximum Nominal Outer Disc Diameter (mm)</th>
<th>Required Introducer Sheath* (Fr)</th>
<th>Recommended Treatable Defect Size Measured with Stop Flow Balloon Sizing (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>10</td>
<td>8-15</td>
</tr>
<tr>
<td>32</td>
<td>10</td>
<td>13-20</td>
</tr>
<tr>
<td>37</td>
<td>11</td>
<td>18-25</td>
</tr>
<tr>
<td>44</td>
<td>12</td>
<td>23-30</td>
</tr>
<tr>
<td>48</td>
<td>14</td>
<td>28-35</td>
</tr>
</tbody>
</table>

* Consider utilizing a long introducer sheath to permit device retrieval of a partially collapsed device within the vasculature, if necessary. If a 0.035” guidewire is utilized, upsizing the introducer sheath by 2 Fr is recommended.

5.5.3. Access Site Management

Closure of the femoral venous puncture site should be performed per hospital standards. Access site hemostasis may be achieved by manual compression or by utilizing alternative methods such as a suture closure device.

5.5.4. Pre-Discharge

Prior to institutional discharge, pre-discharge evaluations will be performed following the schedule of events (section 5.2) if the subject retains the study device (technical success). An ECG and Imaging (TEE, TTE, or ICE) are required at pre-discharge.

5.5.5. Unsuccessful GORE® CARDIOFORM ASD Occluder Procedure

Subjects with unsuccessful placement of a study device (no study device implanted and retained at the conclusion of the index procedure) will be followed through 30 days post-index procedure. Subjects will be contacted by telephone at 30 days; upon completion of this telephone follow-up, the subject will be discontinued from the clinical investigation. These subjects will be considered enrolled and a technical failure for purposes of study analysis.

5.5.6. Post-Procedure Care

At the discretion of the investigator, subjects will be encouraged to limit their physical activities for at least two weeks after study device placement. In uncomplicated cases with satisfactory closure, subjects may be discharged from the hospital as soon as deemed appropriate by the study investigator.

Study Medications Requirements:

Subjects are required to be treated with antiplatelet therapy, such as aspirin and/or clopidogrel bisulfate, for 6 months post-index procedure per the institutional standard of care or physician’s general practice. The decision to continue antiplatelet therapy beyond 6 months is at the discretion of the investigator. In
subjects sensitive to antiplatelet therapy, alternative therapies, such as anticoagulants, should be used for a minimum of 6 months post-index procedure.

Concomitant Medications:

Record only prescription medications. Do not record over-the-counter medications unless prescribed for a specific condition. Do not record daily vitamins or supplements.

5.5.7. Post-Procedure Evaluations and Testing

Post-procedure evaluations will be performed according to the schedule of events (section 5.2). Follow-up information will be recorded in the Clinical Data Management System (CDMS) through the 36-month interval or at the time of subject discontinuation from the clinical investigation.

At post-procedure follow-up intervals (30 days, 6, 12, and 36 months) a TTE is required for all subjects who retained the study device to evaluate defect closure status. The TTE must be completed in accordance with the Echo Core Lab Guidelines. Fluoroscopic examination without contrast (en face and lateral views) will be performed at the 6-month follow-up interval for Training, Pivotal, and Continued Access subjects in order to identify and assess wire frame fracture.

Additional fluoroscopy examination for all enrolled subjects is at the investigator’s discretion. Please refer to the requirements below to determine if fluoroscopic evaluation is required for the subject.

Lack of device stability and/or clinical sequelae identified on follow-up TTE may be indicative of wire frame fractures. All suspected wire frame fracture should be investigated with a fluoroscopic evaluation. All device fractures are reported on the Fluoroscopy CRF. Additionally, device fractures that result in clinical sequelae will be reported as an AE (section 9.0). Chest x-ray is not suitable imaging to evaluate the occluder and defect closure.

Fluoroscopy Requirements

- All subjects (training, pivotal, and continued access) will complete 6-month fluoroscopic imaging. Additional fluoroscopic evaluation should be completed if wire frame fracture is suspected.

All echocardiography and fluoroscopy images obtained at procedural and study follow-up intervals must be recorded in DICOM format according to echocardiographic guidelines provided with this protocol and uploaded to the secure web portal. Baseline and implant images will be reviewed by the Echo Core Lab to assist in evaluating closure progress at subsequent intervals.

At the 24-month interval subjects should be contacted and a telephone questionnaire CRF completed.

All planned and unplanned visits, regardless of etiology, will be documented on CRFs in the CDMS, including reporting of any AEs. It is important that the investigator encourage subjects to return for all required follow-up visits. The clinical investigation objectives may not be realized if a significant number of subjects are lost to follow-up or discontinued prematurely.
5.6. Interventions

Interventions to the study device will be reported on the Intervention CRF. If the study device is removed as part of the intervention, the subject is discontinued from the study. If the study device remains implanted, the subject will continue to be enrolled in the study and will complete study follow-up as prescribed.

5.7. Follow-Up

The follow-up visits should be completed in accordance with the protocol-defined visit windows. The follow-up interval targets are calculated as calendar days from index procedure (Day 0). The visit windows are calculated as the target day ± the appropriate number of calendar days.

<table>
<thead>
<tr>
<th>30 Days</th>
<th>6 Months</th>
<th>12 Months</th>
<th>24 Months</th>
<th>36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 ± 14 days</td>
<td>180 ± 14 days</td>
<td>365 ± 60 days</td>
<td>730 ± 60 days</td>
<td>1095 ± 60 days</td>
</tr>
</tbody>
</table>

A visit completed outside the visit window will be considered a protocol deviation (PD) and should be reported per local IRB policy.

5.8. Subject Withdrawal from the Study

A subject may withdraw from the clinical investigation at any time and for any reason, and should notify the investigator in this event. Subjects are not obligated to reveal their reasons for withdrawal. The subject will be withdrawn if he / she relocates to another geographic area that requires a change of physician and a suitable study investigator cannot be identified.

The investigator may withdraw the subject from the clinical investigation at any time based on his / her medical judgment. It is important that the investigator encourage subjects to return for all required follow-up visits within the designated window.

The investigator or designee must complete the Study Discontinuation Form documenting the subject’s withdrawal or discontinuation from the clinical investigation. The subject will be considered withdrawn once the Sponsor receives this CRF.

If, at any time during the study (other than the index procedure) the GORE® CARDIOFORM ASD Occluder is removed, the subject will be discontinued from further study follow-up. All AEs will be collected and reported in compliance with this protocol through the point of device removal. The investigator or designee will complete the Study Discontinuation Form documenting the subject’s discontinuation from the clinical investigation.

5.9. Subject Lost to Follow-Up

A subject will be considered lost to follow-up and discontinued from the clinical investigation once they have missed more than one follow-up visit and three documented attempts have been made by the investigator or designee to contact the subject or legally authorized representative. One of the three documented attempts must include a certified letter.
5.10. Subject Study Completion

A subject has completed the study when the 36-month follow-up visit has been completed. Any subject who does not complete the 36-month follow-up visit will be considered a discontinuation. Subjects will not be provided with any medical care by the Sponsor after study completion or discontinuation.

5.11. Explant Procedures

The study device may be explanted during a surgical procedure or as part of an autopsy. Investigative sites are requested to return explanted device to the Sponsor for gross and histological evaluation. Prior to planned or potential device retrieval, contact the ASSURED Clinical Study Manager (CSM) to communicate that a specimen is being retrieved from a study subject. A specimen shipping kit will be sent immediately to the site. The specimen kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

5.12. Device Deficiencies

Device deficiencies are defined by ISO 14155 as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Any suspected deficiency with the device should be communicated immediately to the Sponsor.

6. Study Administration

6.1. Training

Participating investigators are required to complete device didactic and protocol training prior to first implant. Each investigational site will be required to complete two training cases prior to enrolling non-training cases in the Pivotal Phase of the study. All investigators participating in the clinical investigation are encouraged to perform or attend the two training cases. Each implanting physician must complete two study device implants observed by a Gore representative or Gore-certified physician proctor to be considered certified to implant the study device.

6.2. Monitoring

Investigative site monitoring for this clinical investigation will be provided by [REDACTED]. Monitoring oversight will be provided by the Sponsor.

The Clinical Monitors are qualified by training and experience to oversee the progress of the clinical investigation at the site and will verify that the investigators and their staff understand and adhere to both the applicable regulatory requirements and the study protocol. In addition, they may assist in resolution of any problems that may arise during the study.

6.2.1. Periodic Site Monitoring

Periodic site visits will occur as necessary to ensure continuing adequacy of facilities and adherence to the clinical study protocol, the Good Clinical Practices (GCPs), and applicable regulations and laws that pertain to the conduct of the clinical investigation. During these visits, the Clinical Monitor will also review the CRFs and source documentation, the timely submission of accurate records to the
Sponsor, and the maintenance of proper records. A report will be written following each investigative site visit and a follow-up letter will be provided to the site with a summary of findings.

6.2.2. Clinical Monitor Reports

The Sponsor’s Clinical Monitor will prepare a written report for the Sponsor following each investigative site visit. Reports will include specific information regarding observations made at the site visit, including staff members consulted, records reviewed, subject enrollment, and general progress of the study, status of any problems identified, any corrective action recommended, and any other information deemed pertinent by the Sponsor’s Clinical Monitor.

6.3. Clinical Investigative Site Initiation Visit

Site initiation will be performed to ensure that each investigator and his/her staff understands the protocol, applicable regulations, human subject protection requirements, and the investigator’s obligations. This visit will ensure that required documentation with the appropriate approval is in place prior to subject enrollment.

6.4. Device Accountability and Storage

The GORE® CARDIOFORM ASD Occluder may be used only under the supervision of the investigator and in strict accordance with this protocol and applicable laws and regulations. The study device may be implanted only in subjects who meet the eligibility criteria set forth in this protocol and consent to participate. The investigator will maintain accurate, detailed records of all devices received from the Sponsor. Information collected on the Device Accountability Log include: date of receipt, catalog number and batch code (Lot # / Serial #), expiration date, date of use, subject identification, the date of return of used and unused devices. The investigator will record and maintain records of each device used on the corresponding CRF and Device Accountability log. The investigator will notify the Sponsor immediately if any devices are damaged or unaccounted for. The devices must be accessible only to the personnel involved in the clinical investigation and stored in a secure facility. Upon completion or termination of the clinical investigation or the investigator’s participation in the clinical investigation, or at the Sponsor’s request, the investigator will return any remaining supply of the device or dispose of the devices as directed by the Sponsor.

6.5. Core Lab

Core lab services for this study will be provided by [supplied by name]. All protocol required imaging will be uploaded to [supplied by name] 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. Please refer to the Echo Core Lab Imaging Guidelines when completing the protocol-specified imaging follow-up exams.

6.6. Protocol Deviations

A protocol deviation (PD) is defined as any change, divergence, or departure in execution from the study design or procedures of a research protocol. The investigator is responsible for promptly recording and reporting PDs to the Sponsor and the reviewing
IRB per IRB policy. The Sponsor will determine the effect of the PD on the scientific soundness of the clinical investigation and subject safety and determine if additional reports or actions are required. Additional action may include site retraining, removal of devices from the site, or removal of the site from study participation.

The investigator will not implement any changes to the protocol without first obtaining written agreement from the Sponsor and documented approval from the IRB, except in the event of an immediate hazard to a subject. The investigator will report the PD in accordance with the applicable regulations.

6.7 Protocol Amendments

The investigator will maintain a copy of the original protocol and all amendments. The investigator will obtain IRB approval on all amendments in a timely manner. The Sponsor will confirm proper training of the investigator and site staff on all protocol amendments, as necessary.

6.8 Sponsor Representatives

Sponsor representatives may be present during study procedures to provide technical assistance to the investigator in the use of the device. The activities of these Sponsor representatives will be supervised by the investigator.

6.9 Access to Source Data/Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the clinical investigation.

The investigator will keep all study records, source data and investigational devices available for inspection by the Sponsor, Sponsor’s Clinical Monitors, IRB, and regulatory authorities.

6.10 Study Records Retention

The investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Records will be maintained during the clinical investigation and for a minimum of two years after the latter of the date on which the clinical investigation is terminated or completed, or the date the records are no longer required to support regulatory approval of the device. In any event, clinical investigation records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but not be limited to:

- All correspondence with another investigator, an IRB, the Sponsor, a Clinical Monitor, or regulatory authority, including required reports.
- Records of receipt, use or disposition of a device that relate to: the type and quantity received, the date of receipt, and lot or batch number, or code mark.
- The names of all persons who received, used, or disposed of each device.
- Records of each subject’s case history and exposure to the device. Case histories include the CRFs and supporting data, such as signed and dated consent forms and medical records, progress notes of the physician, the subject’s hospital chart(s), and the nurses’ notes. Such records shall include: documents evidencing informed
consent and, for any use of a device without informed consent, any written
concurrence of a licensed physician and a brief description of the circumstances
justifying the failure to obtain the informed consent. The case history for each subject
shall document that informed consent was obtained prior to participation in the study.

- All relevant observations, including records concerning adverse device effects
  (anticipated and unanticipated), the information and date and condition of each subject
  upon entering, and information about relevant previous medical history, and the
  results of all diagnostic tests.
- A record of the exposure of each subject to the investigational device, including the
date and time of each use, and any other therapy.
- The protocol, any amendments, and documentation of any deviations from the
  protocol, including the dates and the reasons for such deviations.
- Any other records that the regulatory authority requires to be maintained by regulation
  or by specific requirement for a category of investigations or a particular investigation.
- A certification stating that the IRB is in compliance with regulatory authority
  regulations.
- A signed Investigator Agreement.
- Any other records as required by the regulatory authority, the IRB, and the Sponsor.
- The investigator will prepare and submit the following reports:
  - Withdrawal of IRB approval: the investigator will report any withdrawal of approval
    within 5 working days after the investigator has been notified of the withdrawal.
  - Progress reports: progress reports documenting the procedure, AEs and follow-up
data concerning individual subjects will be submitted to the Sponsor on
  standardized CRFs. The investigator may also be required to submit progress
  reports and final reports to the IRB and to the Sponsor summarizing the
  investigator’s experience during the clinical investigation.
  - Unanticipated Adverse Device Effect (UADE) Reports: UADEs shall be reported as
    described in Section 9.6
  - PDs shall be reported as described in Section 6.6
  - Other: Any other reports as reasonably requested by the Sponsor or required by a
    regulatory authority.

6.11 Publication Plan

The International Committee of Medical Journal Editors (ICMJE) member journals have
adopted a trials-registration policy as a condition for publication. This policy requires that
all clinical trials be registered in a public trials registry. The Sponsor will register the
clinical investigation and post results as required by this policy and applicable U.S. laws
and regulations.

It is the intent of the Sponsor that the multicenter results of this clinical investigation will be
submitted for publication in a peer-reviewed journal. A publications committee will be
established to review the multicenter results and develop publications at the completion of
the clinical investigation. The timing of the multicenter publication may be dependent on
regulatory submissions and approvals. Individual sites should coordinate requests for
publication through the publications committee or the Sponsor.
7. Data Collection and Submission

The CDMS for this clinical investigation will be provided by [REDACTED]. The sponsor keeps a separate Clinical Data Management Plan describing the procedures for verification, validation, and security of the CDMS.

7.1. Data Collection Methods

This study will report clinical data using the [REDACTED] web-based application. The CDMS will be the database of records for the protocol and is subject to regulatory inspections and quality assurance review. All users will be trained to use the CDMS and will comply with study-specific guidelines and instructions as well as applicable regulatory requirements.

Subject data will be collected using protocol-specific CRFs. Site staff will enter data directly into the CDMS for transmission to the Sponsor. The sites will be notified of any significant amendments to the CRFs. No data recorded in the electronic case report form shall be considered source data. Source documentation shall consist of data obtained from the patients’ medical records, imaging or captured on study-specific paper source documents, etc.

7.2. Data Clarification and Correction

Once entered, data will be evaluated to confirm that it is complete, consistent, and logically sound. If changes to the data in the CDMS are required, all changes, reasons for changes, and persons making the changes will be captured in the CDMS’s audit trail.

7.3. CRF Completion Schedule

All CRFs should be completed within 30 days from the date subject visit occurred.

8. Risk Assessment

8.1. Potential Risks

The risks associated with the GORE® CARDIOFORM ASD Occluder for use in transcatheter closure of atrial septal defects are expected to be similar to the risks associated with the use of other commercially available standard-of-care devices.

Possible benefits and risks associated with the study procedures and device placement are outlined in the IRB-approved ICF.

Some risks are possible with transcatheter approaches, including:

- access site complications
- incomplete closure of the ASD
- repeat procedure to the ASD
- air embolism
- myocardial infarction
- pericardial tamponade
- cardiac arrest
- renal failure
- sepsis
• significant pleural or pericardial effusion requiring drainage
• significant bleeding
• endocarditis
• headache or migraine
• transient ischemic attack (TIA) or stroke
• death
• cardiac arrhythmias
• thromboembolic events

Risks specific to the GORE® CARDIOFORM ASD Occluder device include, but are not limited to:
• unsuccessful device delivery
• fracture of the wire frame resulting in device instability or clinical sequelae
• occluder disc expansion resulting in clinical sequelae or intervention
• possible allergic reaction to nickel in wires
• perforation or damage to a cardiovascular structure caused by the device
• enlargement of the defect during or after device deployment
• embolization of the device
• surgical intervention to correct device failure
• insufficient closure of the ASD

8.2. Minimization of Risks

Potential risks associated with the use of the GORE® CARDIOFORM ASD Occluder may be minimized by the following activities:
• The Sponsor has performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production. Investigators will be selected who are knowledgeable and experienced in transcatheter closure of ostium secundum atrial septal defects.
• Comprehensive site investigator and staff training will be conducted to share information regarding design and proper use of the GORE® CARDIOFORM ASD Occluder.
• The site’s Principal Investigator (PI), Sub-Investigators (Sub-I), study coordinator(s) (SC), or designee at each site will be trained to the protocol and subject follow-up requirements.
• Protocol inclusion / exclusion criteria and follow-up schedules are designed to select appropriate subjects and identify potential complications early. Subjects will be assessed post-procedure and subsequently on a regular basis to collect information on the subject’s status and any reportable AEs.
• Sites will be monitored to evaluate protocol compliance and the data for accuracy and subject safety.
• Device performance findings relevant to subject safety discovered during the clinical investigation will be shared with the site investigators to aid understanding of the device and potential complications associated with its use.
• An evaluation will be completed by the investigator for each subject against the inclusion / exclusion criteria before study entry to ensure the subject’s ASD and anatomy are appropriate. Procedural echocardiographic or other appropriate imaging will be used to assess the subject’s ASD suitability.
• Antiplatelet therapy will be prescribed for 6 months post-index procedure to reduce the risk of thrombosis. Peri-procedural antibiotics prophylaxis per the investigator’s standard of care is recommended to reduce the risk of infection.
• All protocol-defined echocardiographic images will be reviewed by the echo core laboratory to evaluate the heart and any residual shunting across the ASD.
• Risk of device embolization has been minimized in two ways. First, the device is designed with a retrieval function. The ability to retrieve the device is maintained until the investigator ensures proper fit into the defect. Additionally, the double disc and adaptable waist design allows physicians multiple options in choosing the correctly sized device for both the defect size and the patient’s surrounding anatomy.
• Defects not smaller than 8 mm and not greater than 35 mm will be treated in this study protocol. As directed in the device IFU and in this protocol, an occluder that pulls through the defect after left or right atrial disc conformation may be too small and should be removed and replaced with a larger size.

8.3 Summary of Expected Benefits

The expected benefit to the patient from the use of the GORE® CARDIOFORM ASD Occluder in the treatment of ostium secundum atrial septal defects is to reduce or arrest the shunting between the atria, to arrest or reverse the associated right heart and pulmonary pathology, and to have a short hospital stay and return to normal activity within two weeks of the procedure.

9. Adverse Events and Safety Monitoring

AEs are defined as any untoward medical occurrences in a subject whether related or not.

9.1 Anticipated Adverse Events

A list of benefits and risks associated with the procedure- and device-related complications that may be anticipated in subjects undergoing transcatheter ostium secundum ASD closure are identified in Section 8.0, Risk Assessment. These pre-defined complications are considered anticipated AEs. If a complication occurs that is not on the list of known, potential complications and the investigator believes that the complication is a potential Unanticipated Adverse Device Effects UADE (see section 9.6), the site should immediately contact the Sponsor to determine reporting requirements.

The investigator at each investigative site is ultimately responsible for reporting AEs to the Sponsor. The investigator or designee is required to complete the appropriate CRFs to report the occurrence of AEs.

9.2 Adverse Event Relationship

Each reported AE will be assessed by the investigator for its primary suspected relationship to the study. Only one primary relationship will be identified for each reported AE.

Related to Study Device

If the functioning or characteristics of the study device or delivery system caused or contributed significantly to the AE, the AE should be reported as primarily related to the study device.
Related to Study Procedure

If the study index procedure (and not the device) caused or significantly contributed to the AE, the AE should be reported as primarily related to the study procedure.

Related to Study Medication

If the AE was a result of the antiplatelet medical therapy required by the study protocol and not the study device or study procedure, the AE should be reported as primarily related to the study medication.

Not Study Related

If an AE cannot be attributed to the study device, study procedure, or study medication, it should be reported as not study related.

9.3. Adverse Event Seriousness Classification

A Serious Adverse Event (SAE) is an AE that satisfies at least one of the following criteria from the ISO 14155 definition of an SAE:

- led to death
  Report if you suspect that the death was an outcome of the AE and include the date, if known.

- led to serious deterioration in the health of the Subject, that resulted in
  - a life-threatening illness or injury
    Report if it is suspected that the Subject was at substantial risk of dying at the time of the AE, or use or continued use of the device or other medical product might have resulted in the death of the Subject.
  - a permanent impairment of a body structure or a body function
    Report if the AE resulted in a substantial disruption of the Subject’s ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent or permanent change, impairment, damage, or disruption in the Subject’s body function or structure, physical activities, or quality of life.
  - In-patient or prolonged hospitalization
    Report if admission to the hospital or prolongation of hospitalization was a result of the AE. Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan (CIP), without a serious deterioration in health is not considered a SAE. Emergency room visits and 23-hour observations do not constitute hospitalization.
    Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage).
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

9.4. Adverse Event Reporting and Coding

AEs will be reported on the appropriate CRF and documented in the subject’s permanent medical record. The investigator at each site is ultimately responsible for reporting AEs to the Sponsor.

The following information on each reported AE will be collected:

- Verbatim description of AE diagnosis. If no diagnosis is available, please report symptoms on separate Adverse Event CRFs
- AE Onset Date
- Primary Relationship (see Section 9.2)
- Seriousness (see Section 9.3)
- Treatment
- Device Action Taken
- Outcome
- AE Resolution Date
- If applicable, whether AE was cause of death.

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

Adverse Event submission guidelines:

- AE reporting begins once the subject is enrolled in the study. All AEs should be reported from enrollment through study completion or 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.
- AEs 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.
- An AE that changes from non-serious to serious should be reported as a new AE.
- Report a new AE if the severity or frequency of a pre-existing condition increases from the baseline condition included in medical history.

9.5 Subject Death

If a subject dies while on the clinical investigation, the cause of death will be reported as the AE and “death” reported as the outcome on the AE CRF. If the subject has other ongoing AEs at the time of death, the outcome status of those AEs should be reported as “death” on each AE CRF with the end date as the date the death occurred.
9.6 Unanticipated Adverse Device Effects

An UADE is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or protocol.

The Sponsor is required to notify the Food and Drug Administration (FDA) within 10 days of any UADE. Therefore, if a complication occurs that the investigator believes may be a potential UADE, the site should immediately contact the Sponsor to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a subject, the site should immediately notify the Sponsor.

The investigator will submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the UADE. All UADEs must be documented by the investigator including the date of onset, a complete description of the event, possible reason(s) for the event, severity, duration, actions taken and outcome. Copies of all supporting documents should be submitted concurrently with the appropriate CRF.

A report from the Sponsor will be submitted to the FDA and to all reviewing IRBs and participating investigators within 10 working days after the Sponsor first receives notice of the UADE.

9.7 Independent Data Review Board (IDRB)

The Sponsor will establish an IDRB. The IDRB will provide external oversight and review for potential safety concerns. The IDRB is composed of physician experts in interventional cardiac therapy who are not participating in the trial.

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.

Any IDRB recommendations for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Sponsor for consideration. However, if the IDRB at any time determines that a potential serious risk exists to subjects in the study, the IDRB will immediately notify the Sponsor.

10. Statistical Analysis

10.1
10.3

10.4. Data Analysis

10.4.1. Timing of Analyses

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

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 status 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.

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

10.4.2. Baseline Characteristics

Subject demographics, clinical history, risk factors, and pre-procedure lesion 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).

10.4.3 Analysis Sets

**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.

**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 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 (test 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.

**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.

**Per-Protocol Analysis Sets**

For per-protocol analysis, only subjects who had no major 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 cause 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.

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

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.
10.4.4. Pooling of Data

The data from all investigative sites will be pooled based on the assumption of clinical comparability; the sites used a common protocol; the sites were adequately monitored 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.

10.4.5. Statistical Analysis of Primary Endpoint(s)

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.

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

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

10.4.6. Sensitivity Analyses

Sensitivity analyses of the co-primary endpoints will be conducted and will include for each, at a minimum, a worst-case analysis and tipping point analysis.

10.4.7. Statistical Analysis of Secondary Endpoint(s)

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.

10.4.8 Additional Analysis

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.

11. Ethical and Regulatory Considerations

11.1 Statement of Compliance

The clinical investigation will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and applicable regulatory requirements.

The following are applicable to this study:

| 21 CFR Part 11 | Electronic Records; Electronic Signatures |
| 21 CFR Part 50 | Protection of Human Subjects |
| 21 CFR Part 54 | Financial Disclosure By Clinical Investigators |
| 21 CFR Part 56 | Institutional Review Boards |
| 21 CFR Part 812 | Investigational Device Exemptions |
| ICH-GCP E6 | International Conference on Harmonisation Regulations Guideline For Good Clinical Practice |

11.2 Compliance Responsibilities

The Sponsor will conduct the clinical investigation in accordance with all applicable regulations and laws. The Sponsor will be responsible for documenting that investigators have the necessary skills, training, and information to properly conduct the clinical investigation. The Sponsor will confirm proper monitoring of the clinical investigation and verify that the site has obtained IRB approval prior to enrollment. The Sponsor will provide information to the investigators, the reviewing IRB, and the FDA concerning the progress of, and any new material information about, the clinical investigation.

The investigator will conduct the clinical investigation in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing IRB and the FDA. The investigator will verify IRB approval is obtained prior to enrollment, maintained throughout the course of the clinical investigation, and that all IRB reporting requirements are met. The investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator’s care and for
the control of devices under investigation. The investigator is also responsible for ensuring that informed consent is properly obtained.

The study shall be conducted in accordance with the ethical principles which have their origin in the Declaration of Helsinki.

11.3 Informed Consent

The investigator shall verify that all potential subjects for this study are provided with a consent form describing this clinical investigation and sufficient information to make an informed decision about their participation.

The formal consent of a subject, using the IRB-approved consent form, must be obtained by the investigator before that subject undergoes any study-related procedure. The consent form will be signed and personally dated by the subject or legally authorized representative, and the person who conducted the informed consent discussion. The original signed ICF will be retained in the subject records. A copy of the informed consent document will be given to the subject for his or her records. Any significant, new information which emerges while the clinical investigation is in progress that may influence a subject’s willingness to continue to take part in the clinical investigation will be provided to the subject.

The investigator shall verify that documentation of the acquisition of informed consent is recorded in each subject’s records in accordance with applicable regulations.

11.4 Independent Ethical Review

The investigator shall not enroll any subjects prior to obtaining approval for the clinical investigation from a properly constituted independent IRB.

The investigator will submit the protocol, ICF, other information to be provided to subjects, such as survey instruments or questionnaires, and any proposed advertising or recruitment materials, to the IRB for written approval.

11.5 Conflict of Interest

All investigators will follow applicable laws and regulations as well as the conflict of interest policies of their sites and the reviewing IRBs.

Investigators will provide the Sponsor with sufficient accurate financial disclosure information to allow the Sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. Investigators will promptly update this information if any relevant changes occur during the course of the clinical investigation and for one (1) year following completion of the clinical investigation.

11.6 Confidentiality

All subject records will be kept confidential to the extent provided by applicable laws and regulations. The Clinical Monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records.
Such records may also be reviewed by the site’s IRB and other regulatory bodies (e.g., FDA).

The investigator will inform the subjects that their records will be reviewed.

11.7. Emergency / Compassionate Use

There are circumstances where the GORE® CARDIOFORM ASD Occluder Device may provide an investigator the ability to save a patient’s life or prevent serious morbidity of which there is no reasonable alternative medical treatment available. Gore will support use of the GORE® CARDIOFORM ASD Occluder Device, in an emergency or compassionate use fashion, provided that the applicant site provides all required information to support its use and meets all regulatory guidelines. Patients who qualify for emergency / compassionate use shall follow the Informed Consent Process as outlined in section 11.3. Patients who receive the study device in this fashion will not be included in the analysis of safety or effectiveness endpoints. Sites using this regulatory mechanism will be expected to meet all requirements following the procedure in terms of reporting to their IRB, Gore and hospital administration (where applicable). It will be the responsibility of the sites to evaluate these patients and report any device events to Gore when they become aware of its occurrence.

11.8. Study Discontinuation or Suspension

The entire study may be suspended or prematurely terminated by the sponsor in the following cases:

- Serious adverse events as defined in section 9 attributable to the investigation.
- If new data become available which raises concern about the safety of the study device, so that continuation of the study might cause unacceptable risks to the subjects.
- If suspicion of an unacceptable risk to subjects arises during the clinical investigation, the sponsor may suspend the clinical investigation while the risk is assessed. The sponsor will terminate the clinical investigation if an unacceptable risk is confirmed.
- National regulatory authority withdrawal of study approval.
- On recommendation by the IDRB for any perceived safety concern based on clinical judgment, including, but not limited to, a higher than anticipated rate for any component of the safety endpoint, device failures resulting in AEs or unexpected SAEs.
- Administrative decision by the sponsor.

Study participation of an individual study site or an individual member of a study site may be suspended or prematurely terminated by the sponsor in the following cases:

- If a principal investigator, IRB or regulatory authority responsible for the study has withdrawn approval for any reason.
- If sponsor monitoring or auditing identifies serious or repeated deviations on the part of the study site or an individual study investigator.
- If a site does not enroll any subjects.
Procedures for suspension or premature termination of this study are:

- If the sponsor, IRB or regulatory authority suspends or prematurely terminates the study, all enrolled subjects shall continue to be followed and treated as per standard of care at each site. The sponsor may request that subjects are contacted or complete an office visit prior to study termination.
- The investigator or each site or authorized designee shall promptly inform the enrolled subjects.
- If the sponsor received notice that the IRB and/or regulatory authority approval has been withdrawn for any reason, the sponsor shall notify the investigator as soon as possible and preferably within 24 hours. Study enrollment must immediately cease until such approval is reinstated.
- If the investigator receives notice that the IRB and/or regulatory authority approval has been withdrawn for any reason, the investigator shall notify the sponsor as soon as possible and preferentially within 24 hours. Study enrollment must immediately cease until such approval is reinstated.
- If the sponsor suspends or prematurely discontinues the study the sponsor shall inform the investigators, the IRB’s and the authority of the rationale and provide them with the relevant data supporting this decision.
- If the study (or a study site) is prematurely terminated, a routine close out visit will be performed.

The procedures of premature study termination of an individual subject (voluntary withdrawal or withdrawal of the subject by the investigator) are detailed in section 5.8 of the study protocol.

Procedure for resuming the clinical investigation after temporary suspension

- When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall obtain concurrence from the IRB’s and, where appropriate, the regulatory authority by providing the rational and relevant data supporting this decision before the clinical investigation resumes.
- When concurrence from IRB’s and, where appropriate, other regulatory authorities is obtained, the sponsor shall inform the investigators to resume the clinical investigation.
- If subjects have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.
Protocol Modification Summary

List of Changes in: **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)**

**Amendment #1**

The following administrative changes have been made to the protocol:
- Minor typographical and punctuation errors have been corrected throughout the protocol.
- In addition, the following changes have been made to the protocol:

<table>
<thead>
<tr>
<th>Section</th>
<th>Changes to Protocol</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Summary</td>
<td>Added Coordination PI's</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
<tr>
<td>Protocol Summary</td>
<td>Number of sites changed from 30 to 22</td>
<td>Per revised FDA IDE approval letter 03-Jan-2017</td>
</tr>
<tr>
<td>Protocol Summary</td>
<td>Added Pre-discharge assessments to Schedule of Events</td>
<td>For protocol consistency</td>
</tr>
<tr>
<td>Title page</td>
<td>Added protocol date</td>
<td>Internal review process suggest change</td>
</tr>
<tr>
<td>Section 1.2 – Study Device Description</td>
<td>Added manufacture details and description on where to find additional information</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
<tr>
<td>Section 3.2 – Description of Study Design</td>
<td>Number of sites changed from 30 to 22</td>
<td>Per revised FDA IDE approval letter 03-Jan-2017</td>
</tr>
<tr>
<td>Section 4.1– Description of population</td>
<td>Added definition of vulnerable patient population for children and recommendation for IRB compliance</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
</tbody>
</table>
| Section 5.1 – Study Procedures and Evaluation Schema | Updates to study schema:  
  - Added Enrollment CRF to Screen Failure requirements  
  - Added AE Assessment (if any) to Technical Failure subject follow up  
  - Revised language to Subjects who have study device removal after completion of index procedure to be consistent with Section 5.6, 5.8 of study protocol | For protocol consistency |
<table>
<thead>
<tr>
<th>Section</th>
<th>Changes</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 5.2 Schedule of Events</td>
<td>Added ** Fluoroscopy at pre-discharge is per Investigator discretion</td>
<td>For protocol consistency</td>
</tr>
<tr>
<td>Section 5.5.4 – Pre-Discharge</td>
<td>Added text regarding the ECG required at pre-discharge.</td>
<td>For protocol consistency</td>
</tr>
<tr>
<td>Section 5.12– Device Deficiencies</td>
<td>Added ISO definition of device deficiencies and reporting instructions</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
<tr>
<td>Section 6.4 – Device Accountability and Storage</td>
<td>Added description of traceability of the study device by using the DA log</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
<tr>
<td>Section 6.5– Core Lab</td>
<td>Updated name of Imaging Vendor to from [REDACTED] to [REDACTED]</td>
<td>Vendor [REDACTED] acquired by [REDACTED]</td>
</tr>
<tr>
<td>Section 6.6 – Protocol Deviations</td>
<td>Removed requirement of reporting protocol deviations on protocol deviation log</td>
<td>Updated protocol deviation reporting requirements to notify Sponsor and monitor when protocol deviation occurs</td>
</tr>
<tr>
<td>Section 7 – Data Collection and Submission</td>
<td>Added procedures for verification, validation and securing of the electronic clinical data systems.</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
<tr>
<td>Section 8.1 – Potential Risks</td>
<td>Added risk “perforation or damage of a cardiovascular structure by the study device”</td>
<td>Clarification of a known risk</td>
</tr>
<tr>
<td>Section 11.2 – Compliance Responsibilities</td>
<td>Added statement that the clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
<tr>
<td>Section 11.7– Emergency / Compassionate Use</td>
<td>Added plan for emergency /compassionate use of the device</td>
<td>Added</td>
</tr>
<tr>
<td>Section 11.8– Study Discontinuation or Suspension</td>
<td>Added plan for discontinuation or suspension of the study</td>
<td>Added per ISO14155:2011 compliance</td>
</tr>
</tbody>
</table>
Protocol Modification Summary

List of Changes in: 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)
Amendment #2

The following administrative changes have been made to the protocol:

- Minor typographical and punctuation errors have been corrected throughout the protocol.
- In addition, the following changes have been made to the protocol:

<table>
<thead>
<tr>
<th>Section</th>
<th>Changes to Protocol</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Summary</td>
<td>Revised Total Study Enrollment: Up to 504 subjects</td>
<td>125 Pivotal subjects + up to 335 Continued Access subjects + 44 Training subjects at 22 sites = Up to 504 subjects</td>
</tr>
<tr>
<td>Protocol Summary</td>
<td>Added: Fluoroscopy requirement at 6 months for Training, Pivotal and Continued Access Subjects</td>
<td>Fluoroscopy requirement added for Continued Access subjects in Amendment 2</td>
</tr>
<tr>
<td>Section 3.1 – Study Design Schema</td>
<td>Revised Overall study cohort to “up to 504 subjects”</td>
<td>For protocol consistency</td>
</tr>
</tbody>
</table>
| Section 5.1 – Study procedures and evaluations schema | Updates to study schema:  
  - Added fluoroscopy requirement at 6 months for Technical Success Continued Access Subjects | For protocol consistency                                                                                      |
<p>| Section 5.2 – Schedule of events | Removed: Asterisk on Fluoroscopy at 6 months that restricted it to Training and Pivotal subjects only. | Fluoroscopy requirement added for Continued Access subjects in Amendment 2                                      |</p>
<table>
<thead>
<tr>
<th>Section 5.5.7 - Post-Procedure Evaluations and Testing</th>
<th>Added: Fluoroscopic examination without contrast (en face and lateral views) will be performed at the 6-month follow-up interval for Training, Pivotal, and Continued Access subjects in order to identify and assess wire frame fracture.</th>
<th>For protocol consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 5.5.7 - Post-Procedure Evaluations and Testing</td>
<td>Added: All Subjects (training, pivotal and continued access) will complete 6-month fluoroscopic imaging. Additional fluoroscopic evaluation should be completed if wire frame fracture is suspected.</td>
<td>For protocol consistency</td>
</tr>
<tr>
<td>Section 5.5.7 - Post-Procedure Evaluations and Testing</td>
<td>Removed: Subject IDs with 301-399 numbers (Continued Access subjects) should complete fluoroscopic evaluation if wire frame fracture is suspected. Institutional subject records or documents from a referring institution or physician (such as catheterization report, discharge summary, or echocardiographic transcription) should not be forwarded to the Sponsor. Necessary records should be available for scheduled monitoring by the Contract Research Organization (CRO) on the Sponsor's behalf. Documentation for AEs may be requested.</td>
<td>For protocol consistency as Fluoroscopy is required for all technical success subjects at 6 months</td>
</tr>
</tbody>
</table>
Protocol Modification Summary

List of Changes in: **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)**

**Amendment #3**

The following administrative changes have been made to the protocol:

- Typographical and punctuation errors have been corrected throughout the protocol.
- In addition, the following changes have been made to the protocol:

<table>
<thead>
<tr>
<th>Section</th>
<th>Changes to Protocol</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol Summary</td>
<td>Revised Total Study Enrollment: Up to 704 subjects</td>
<td>125 Pivotal subjects + up to 535 Continued Access subjects + 44 Training subjects at 22 sites = Up to 704 subjects</td>
</tr>
<tr>
<td>Section 3.1 – Study Design Schema</td>
<td>Revised Total Study Enrollment: Up to 704 subjects</td>
<td>125 Pivotal subjects + up to 535 Continued Access subjects + 44 Training subjects at 22 sites = Up to 704 subjects</td>
</tr>
<tr>
<td>Section 3.2 - Description of Study Design</td>
<td>Revised Total Study Enrollment: Up to 704 subjects</td>
<td>125 Pivotal subjects + up to 535 Continued Access subjects + 44 Training subjects at 22 sites = Up to 704 subjects</td>
</tr>
</tbody>
</table>