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

Protocol Number: GSO 10-09

Original Protocol: 26 June 2012

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Study Information

Study Title	GORE® Septal Occluder Clinical Study: A Study to evaluate safety and efficacy in the treatment of transcatheter closure of *ostium secundum* atrial septal defects (ASDs)
Protocol Number	GSO 10-09
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 4250 West Kiltie Lane Flagstaff, AZ 86005 Telephone: 800-437-8181 Facsimile: 928-864-4957
Study Design	Prospective, mulitcenter, single-arm, clinical study comparing the GORE® Septal Occluder to outcomes from previous GORE® HELEX Septal Occluder clinical studies.
Study Objective	To evaluate the safety and efficacy of the GORE® Septal Occluder in the treatment of percutaneous, transcatheter closure of *ostium secundum* atrial septal defects (ASDs).
Study Endpoints	Primary Endpoint Composite Clinical Success evaluated at 6 months post-procedure Secondary Endpoints • Technical Success • Procedure Success • Closure Success • Safety
Patient Population	Patients with: • *ostium secundum* atrial septal defects of ≤17 mm measured by stop flow balloon sizing • evidence of right ventricular volume overload • absence of concurrent cardiac defect(s) that could elevate morbidity/mortality beyond what is common for ASD (e.g. Large ventricular septal defect, hypoplastic left heart syndrome, coarctation, arrhythmias requiring electrophysiology or concurrent intervention with device placement)
Number of Sites	Up to 21 sites
Enrollment	400 total subjects in following phases: 50 Pivotal 350 Continued Access Post Approval (if required)
Study Duration	Enrollment Duration: Pivotal Phase: 7 months Continued Access Phase: 12-20 months Post Approval Phase: (if required post PMA approval)

	Pivotal Study Duration: 13-16 months Overall Study Duration: 5-6 years based on 36 months follow up for enrolled subjects
Pre-Enrollment Evaluation	Pre-procedural exam performed within 6 months of procedure that must include: ▪ confirmation of ASD by TTE or TEE ▪ estimated defect size ≤17mm ▪ ECG Subjects will be considered enrolled when the GORE® Septal Occluder device is introduced into the anatomy of the subject.
Follow-Up Evaluations	Subjects successfully enrolled in the study will be examined at 30 days and 6 months after the procedure. Each visit will include: ▪ physical exam ▪ ECG ▪ TTE ▪ Fluoroscopy-En face and lateral views (6 months)* Long term follow-up will be performed at 12, 24 and 36 months. The 12 and 36 month visits will include: ▪ physical exam ▪ ECG ▪ TTE ▪ Fluoroscopy-En face and lateral views (36 months)* The 24 month visit by telephone follow-up questionnaire. * Refer to Section 5.4.8 for details.
Echocardiographic Core Laboratories	Craig Fleishman, MD, FACC, FASE Director, Non-Invasive Cardiac Imaging Arnold Palmer Hospital for Children Orlando FL Ricardo Pignatelli, MD Assistant Professor Pediatrics Texas Children's Hospital Baylor College of Medicine Pediatric Cardiology Houston TX
Study Clinical Monitor	Theorem Clinical Research Telephone: 800.290.5766 www.theoremclinical.com
IDE or PMA Number	G110161

LIST OF ABBREVIATIONS

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

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1.0 Introduction

W. L. Gore & Associates, Inc., has developed an atrial septal defect (ASD) closure device, the GORE® Septal Occluder. This minimally invasive occluder device is intended to effectively repair *ostium secundum* ASDs.

Ostium secundum atrial septal defects 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 U.S. alone it is estimated that approximately 10,000 new patients per year can be expected to have an ASD. Successful surgical repair of ASD has been performed for 50 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.

The primary objective of the GORE® Septal Occluder Study is to evaluate the safety and efficacy of the occluder device in the treatment of transcatheter closure of *ostium secundum* atrial septal defects (ASDs). The data obtained in this study will evaluate this next generation device as compared to outcomes of prior studies conducted with the GORE® HELEX® Septal Occluder.

1.1 Device Description

1.1.1 GORE® Septal Occluder

The GORE® Septal Occluder consists of an implantable occluder and a catheter delivery system. The occluder is comprised of five platinum-filled nickel-titanium (Nitinol) wires which form a frame covered with expanded polytetrafluoroethylene (ePTFE). The ePTFE is treated with a hydrophilic coating to facilitate echocardiographic imaging of the occluder and surrounding tissue during implantation. When fully deployed, the occluder assumes a configuration (see Figure 1) to prevent shunting of blood between the right and left atria.

The occluder is configured in nominal diameters of 15, 20, 25, and 30mm. The occluder is delivered using conventional catheter delivery techniques and may be delivered with the aid of a 0.035" guidewire, or smaller, if necessary.

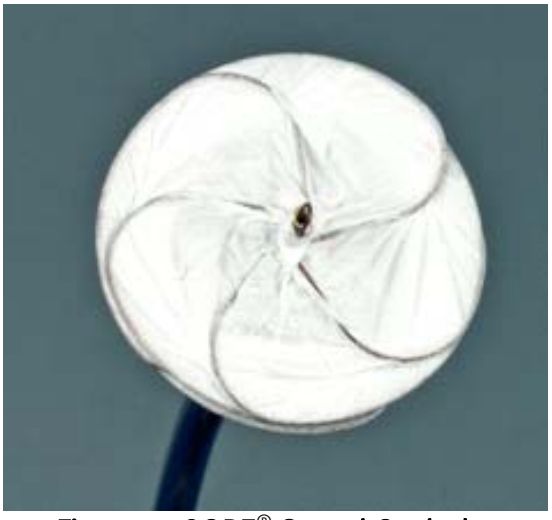


Figure 1: GORE® Septal Occluder

1.2 GORE® Septal Occluder Delivery System

The delivery system consists of a 75 cm working length 10 Fr (O.D.) delivery catheter, a control catheter, and a mandrel coupled to a handle (Figure 2). The handle facilitates loading, deployment, and locking of the occluder. The handle also allows repositioning and retrieval of the occluder via the retrieval cord, if necessary.

The catheter delivery system for the GORE® Septal Occluder is a catheter and handle assembly composed of four primary components.

- Delivery Catheter: Delivers the occluder to the treatment site.
- Control Catheter: Advances/retracts the occluder at the treatment site.
- Mandrel: Supports the Nitinol frame and the locking mechanism of the occluder.
- Handle: Facilitates simple push/pull motions for occluder loading, deployment, and locking.

The catheter components are arranged coaxially and are coupled to the handle mechanism. The handle moves the catheter components separately or in combination to facilitate simple push/pull motions for occluder loading, deployment, and locking. The retrieval cord attaches the proximal eyelet of the occluder to the control catheter and facilitates occluder retrieval after lock

release, if necessary. A flexible flushing port is attached to the handle to permit convenient device flushing prior to implant.

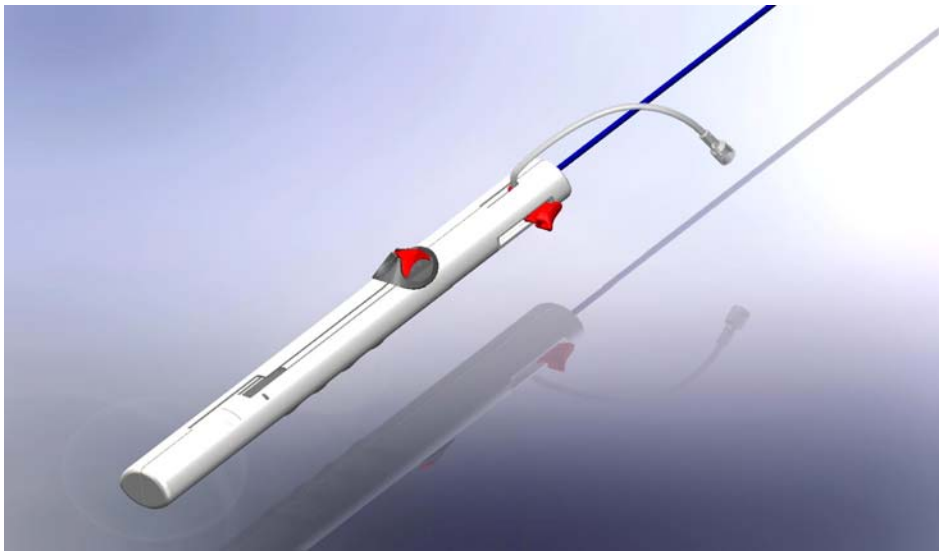


Figure 2: GORE® Septal Occluder Handle Delivery System

2.0 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and effectiveness of the GORE® Septal Occluder when used for percutaneous, transcatheter closure of *ostium secundum* atrial septal defects (ASDs).

3.0 Study Design

3.1 Description of Study Design

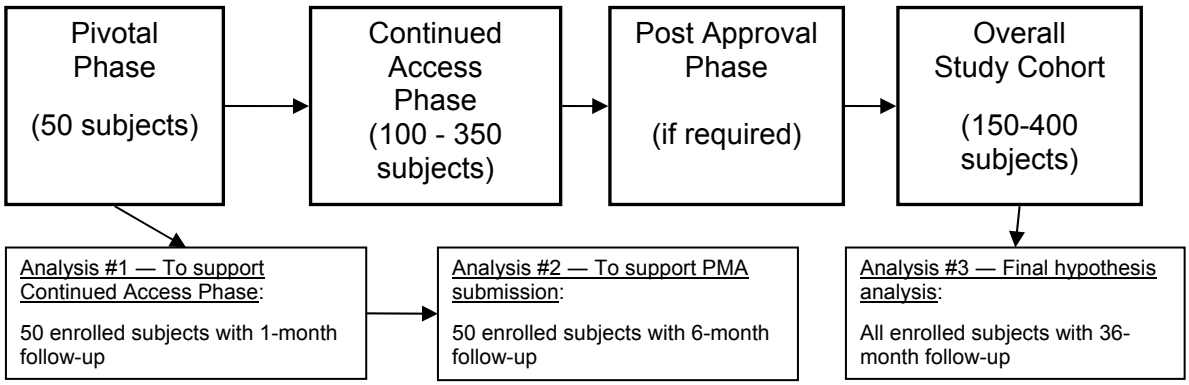
This is a prospective, multicenter, single arm, clinical study comparing outcomes with the GORE® Septal Occluder to outcomes from previous GORE® HELEX® Septal Occluder clinical studies.

This study will enroll 150 - 400 subjects from a maximum of 21 sites. Enrollment will occur in three phases – Pivotal (50 subjects), Continued Access (100 - 350 subjects), and Post Approval (if required). Each phase will enroll sequentially (see Study Schema). Criteria for initiation of each phase of enrollment are presented in Section 10.5.

All enrolled subjects will be followed through the 36-month, post index procedure follow-up. The study primary endpoint, composite Clinical

Success, will be evaluated at 6 months post index procedure. The analysis in support of pre-market approval submission will occur when the 50 Pivotal subjects have completed 6-month follow-up evaluations. The final, primary endpoint analysis of Clinical Success will occur when all enrolled subjects have completed 36-month follow-up evaluations.

Study Schema



3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint for the study is composite Clinical Success evaluated at 6 months post index procedure and is defined as satisfying all the following criteria:

1. Successful deployment and retention (at conclusion of index procedure) of a GORE® Septal Occluder
2. Freedom from:
    - any Serious Adverse Event (SAE) through 30 days post procedure
    - device events (post-procedure embolization, device removal, or other device reintervention) from completion of the implant procedure through the 6-month follow-up evaluation
3. A clinical residual defect status of completely occluded or clinically insignificant residual shunt at 6-month evaluation as determined by the Echo Core Lab (see Section 3.2.3)

3.2.2 Secondary Endpoints

Technical Success: Successful deployment and retention of a GORE® Septal Occluder device at the conclusion of the index procedure.

Procedure Success: Technical Success with the GORE® Septal Occluder and ≤2mm residual shunt of the target ASD at conclusion of the index procedure.

Closure Success (Efficacy): Technical Success and measured residual defect status of occluded/trivial, evaluated at 6 months, 12 months, and 36 months post index procedure.

Safety: A calculation of the proportion of subjects experiencing one or more Serious Adverse Event(s) (SAE) in the first 30 days post index procedure and/or a device event (embolization, device removal, reintervention after completion of index procedure) through 6 months, 12 months, and 36 months post index procedure.

3.2.3 Study Definitions

Clinical Residual Defect Status – categories defined based on clinical characteristics of the residual shunt at study follow-up intervals as determined by the echocardiography core lab:

1. **Completely Occluded**, defined as absence of residual shunt
2. **Clinically Insignificant Residual Shunt**, defined as all of the following:
    a. Residual shunt is hemodynamically insignificant based on any of the following characteristics:
        i. Normalization of ventricular septal motion
        ii. Significant decrease in right ventricular size as determined by comparison of equivalent parasternal and apical images of the right ventricle pre- and post-device placement
    b. No clinical sequelae related to the leak
3. **Clinically Significant Residual Shunt**, defined as any of the following:
    a. A residual left to right shunt or right heart volume overload that would likely require repeat intervention
    b. Clinical sequelae related to the leak
    c. Hemodynamically significant, defined as failure to meet criteria for hemodynamically insignificant detailed above

Measured Residual Defect Status – If present, residual defect size 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:

1. Occluded = absence of residual shunt
2. Trivial = ›0 to ≤2mm residual shunt

3. Moderate = ›2 to ≤4 mm residual shunt
4. Large = ›4 mm residual shunt

4.0 Description of Population

Subjects with an *ostium secundum* ASD having a stop flow balloon diameter of less than or equal to 17 mm may be enrolled. Baseline variables are assessed by means of physical examination, electrocardiogram (ECG), and transthoracic or transesophageal echocardiography (TTE or 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. Overall health, age and other underlying conditions should be considered prior to patient enrollment.

Only patients who meet all of the Inclusion Criteria and none of the Exclusion Criteria will be enrolled.

4.1 Inclusion Criteria

All responses must be *Yes* to be eligible.

1. Patient has an *ostium secundum* ASD with evidence of right ventricular volume overload.
2. Patient has a defect size of ≤17 mm as measured directly by stop flow balloon sizing.
3. Patient vasculature is able to accommodate the delivery system and/or procedural accessories.
4. Patient is able to accommodate TEE or ICE probe for implant procedure.
5. Patient is judged to have adequate septal rims to retain the device.
6. Patient (or legal guardian, if subject is a minor) must voluntarily sign a Patient Informed Consent Form specific to the study. The Patient Informed Consent Form must be reviewed and approved in a manner that complies with requirements of the hospital's Institutional Review Board.
7. Patient (and legal guardian, if patient is a minor) must be physically and mentally willing to comply with all study follow-up

requirements through 36 months, including routinely scheduled diagnostic testing and physical examinations.

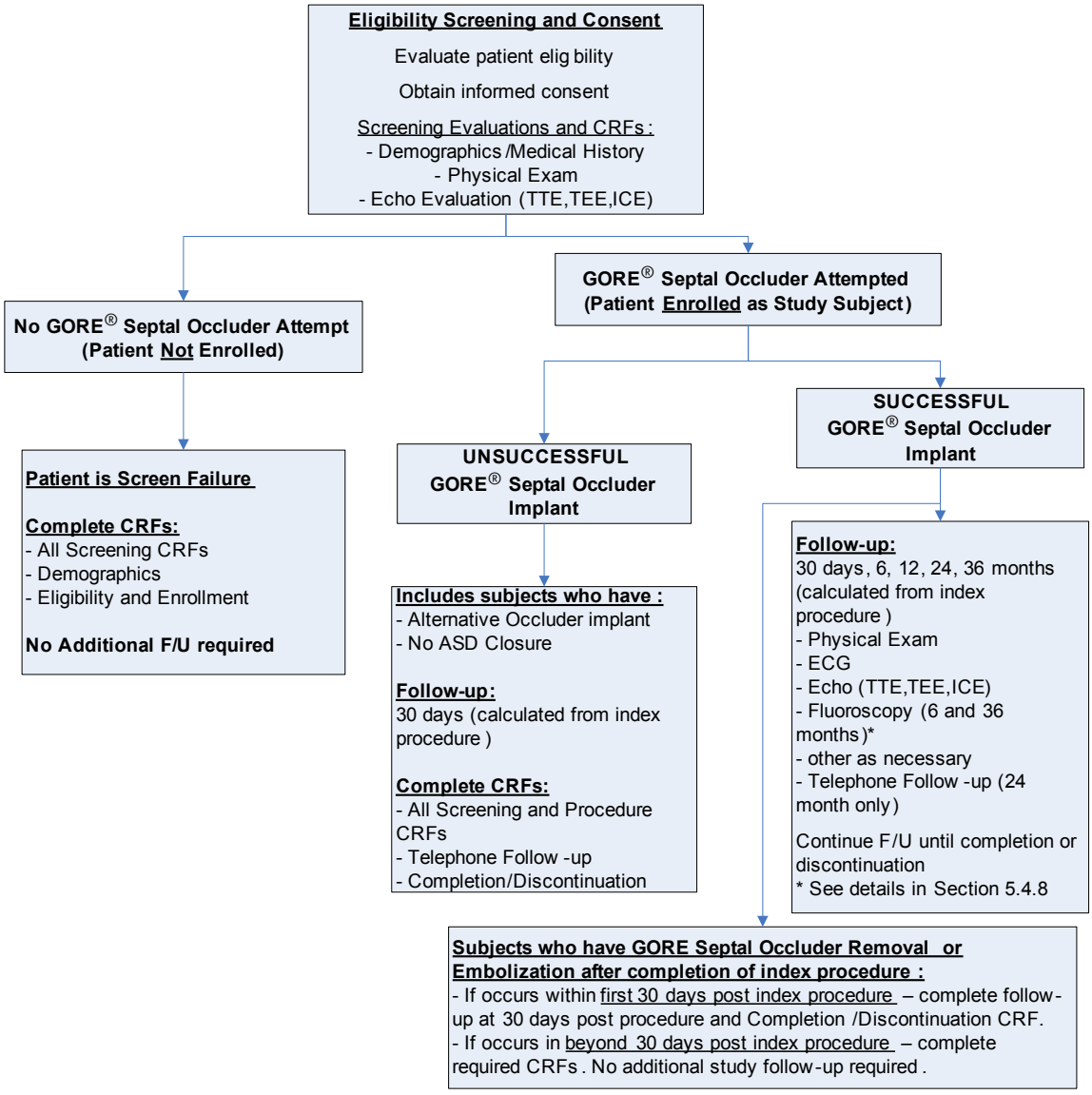
4.2 Exclusion Criteria

All responses must be *No* to be eligible.

1. Patient has significant known pre-existing electrophysiologic, structural cardiovascular defect, or other comorbidities that could elevate morbidity/mortality beyond what is common for ASD or that is expected to 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, arrhythmias requiring electrophysiology study, or intervention concurrent with device placement.
2. Patient has systemic or inherited conditions that would significantly increase subject risk of major morbidity and mortality during the term of the study. Examples would be endocarditis, cancer, degenerative neuromuscular disorder, cardiomyopathy, or 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 in other intracardiac or intravasculature 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 one (or more) known intracardiac thrombi.
6. Patient has an uncontrolled arrhythmia.
7. Patient has a history of stroke resulting in a significant morbidity or disability.
8. Patient is pregnant or lactating at time of enrollment.
9. Patient has contraindication to antiplatelet therapy.
10. Patient has a pulmonary artery systolic pressure greater than half the systemic systolic arterial pressure unless the indexed pulmonary arteriolar resistance is ‹5 Woods units.
11. Patient has multiple defects based on screening imaging and stop flow balloon sizing that would require placement of ›1 device.

5.0 Study Procedures and Evaluations

5.1 Study Evaluations Schema



5.2 Schedule of Events

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

Procedure / Evaluation	Screening/ Pre-procedure (within 6 mo of index procedure)	Procedure	Pre-discharge	Unsuccessful Implant – 30 Days (day 30: ± 14 days)	30 Days (day 30; ± 14 days)	6 Months (day 180: ± 14 days)	12 Months (day 365 ± 60 days)	24 Months (day 730; ± 60 days)	36 Months (day 1095 ± 60 days)
Screening Evaluation and estimated defect size* (TTE, TEE or ICE)	X								
Patient Informed Consent & HIPAA	X								
Demographics and Medical History	X								
Physical Exam	X	X			X	X	X		X
TTE/TEE/ICE (subcostal, parasternal, and apical 4-chamber views)		X	X		X	X	X		X
ECG	X		X		X	X	X		X
Antiplatelet Therapy		X	X		X	X			
Telephone Questionnaire				X				X	
Assess Adverse Events		X	X	X	X	X	X	X	X
Fluoroscopy (without contrast; Enface and lateral views)**						X**			X**

* performed within 6 months prior to index procedure

** Only if clinically indicated for certain subjects. Refer to Section 5.4.8 for details

5.3 Informed Consent Process

All patients must provide informed consent, or assent for minors, prior to any study related procedures being performed. The case history (i.e. source documents/subject chart) for each subject must document that such informed consent was obtained. The patient, and authorized representative when applicable, must sign and date the informed consent form (ICF). The Investigator or designee must also sign the ICF. The patient will be provided with a copy of the signed and dated ICF and the original will be maintained at the Investigator site.

5.4 Screening/Pre-treatment, Enrollment, Procedure, and Follow-up

In all cases, the Investigator maintains exclusive responsibility for the inclusion and exclusion of any potential study participant(s). 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 study, the necessary medical history, physical exam and inclusion/exclusion criteria are reviewed. If the patient meets the criteria for entry into the study, the *Patient Informed Consent Form* is administered.

A screening evaluation is performed within six (6) months of procedure to identify initial suitability of defect closure. This pre-treatment patient evaluation will assess eligibility variables by means of physical examination, electrocardiogram (ECG) and transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) or other appropriate imaging to estimate static defect size of 17 mm or less may be enrolled. Peri-procedural antibiotics may be prescribed at the discretion of the Investigator.

Subjects with additional cardiac conditions anticipated to require surgery within three (3) years of enrollment are not permitted in the study. In addition, no concurrent intervention(s) should be performed during the occluder procedure.

5.4.2 Screen Failure

Patients who consent to participate in the study, but who are determined to not have suitable anatomy and no GORE® Septal Occluder implant or placement is attempted, will be considered screen failures and will not be followed in this study (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 EDC system.

5.4.3 Enrollment

A subject is considered enrolled into the clinical study when the GORE® Septal Occluder device is introduced into the anatomy of the subject. Subjects who enroll in the trial and have a successful implant should be followed through 36 months post index procedure (see Study Schema, Section 5.1).

5.4.4 Transcatheter Procedure

Subjects will be consented to the GORE® Septal Occluder Study prior to transcatheter procedure.

Subjects will undergo placement of the GORE® Septal Occluder via a transcatheter procedure. During the transcatheter procedure either transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) will be performed with general anesthesia or conscious sedation based on the institution or Investigator's general practice. These are acceptable testing modalities during the transcatheter procedure. Procedure time begins upon venous cannulation and procedure time ends upon removal of the final catheter.

At that time, under general anesthesia or conscious sedation and by utilizing transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE), either TEE or ICE static sizing and stop flow balloon sizing of the defect takes place. Static and stop flow balloon defect sizing of 17 mm or less and cardiac anatomy will determine final patient suitability and the appropriate device size for closure of the defect.

Data will be recorded to characterize the procedure.

5.4.4.1 Recommended Procedure Technique (Instructions for Use)

Detailed Instructions for Use for placement of the GORE® Septal Occluder may be found in the GORE® Septal Occluder package as well as in Study Regulatory Binder.

The following recommendations should be considered when choosing the appropriate GORE® Septal Occluder for the subject:

1. The selected occluder nominal diameter should be in a range reflecting 1.75 times the stop flow diameter of the defect (1.75:1 ratio of device nominal diameter-to-defect diameter).
2. The defect should be evaluated to ensure there are adequate septal rims to retain the device.

3. The occluder size and position should be evaluated to ensure no interference with other intracardiac or intravavular structures, such as cardiac valves or pulmonary veins.
4. If successful deployment cannot be achieved after three (3) attempts, an alternative treatment for ASD closure is recommended. Consideration should be given to the patient's total exposure to radiation if prolonged or multiple attempts are required for placement of the occluder.
5. Removal of the occluder should be considered if:
    - Lock loop does not capture all three eyelets;
    - Occluder will not come to rest in a planar position apposing the septal tissue;
    - Occluder allows excessive shunting; or
    - Impingement on adjacent cardiac structures is observed.

Expansion of an occluder disc may occur in the periprocedural time period. If there is uncertainty that an expanded device remains locked, fluoroscopic examination without contrast is recommended in order to identify if the Lock Loop captures all three eyelets.

5.4.4.2 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.

5.4.5 Pre-Discharge

Prior to institutional discharge, pre-discharge evaluations will be performed following the schedule of events (section 5.2). Imaging required is either transesophageal or transthoracic echocardiography (TEE/TTE) or intracardiac echocardiography (ICE).

5.4.6 Unsuccessful GORE® Septal Occluder Procedure

Subjects with unsuccessful placement of a GORE® Septal Occluder (no study device implanted at conclusion of index procedure) will be followed through 30 days post index procedure. Subjects will be contacted by phone at 30 days for follow-up; upon completion of the telephone follow-up Case Report Form (CRF) at the 30-day Unsuccessful Implant interval, subject is discontinued from the study. These subjects will be considered enrolled and a technical failure for purposes of study analysis.

5.4.7 Post-Procedure Care

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

Patients 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.

5.4.8 Post-Procedure Evaluations and Testing

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

At post-procedure follow-up intervals (30 days, 6, 12, and 36 months) a TTE or TEE is required for all subjects with the GORE® Septal Occluder to evaluate defect closure status.

Fluoroscopic examination without contrast (En face and lateral views) will be performed at the 6 and 36 month intervals in order to identify and assess wire frame fractures. Please refer to the requirements below to determine if fluoroscopic evaluation is required for subject, or only necessary if clinically indicated.

Lack of device stability may be indicative of wire frame fractures. All device fractures are reported on the Subject Follow-up Evaluation CRF. Additionally, device fractures that result in device removal because of device instability or other clinical sequelae will be reported as adverse events. Chest x-ray is not suitable imaging to evaluate the occluder and defect closure.

Fluoroscopy Requirements

- Subject IDs referenced with 100 and 200 numbers within the study database must complete 6 and 36 month fluoroscopic imaging. These are the first 150 subjects enrolled (50 Pivotal and 100 Continued Access).
- Subject IDs with 300 numbers, fluoroscopic images are optional and only recommended in subjects where device stability is questionable at any follow up interval. Subjects

enrolled with 300 numbers begin with the 151st enrollment through the time of PMA approval.

Institutional subject records or documents from a referring institution or physician (i.e., 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 adverse events may be requested.

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 BioClinica WebSend 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 in the CDMS system, including reporting of any adverse events. It is important that the Investigator encourage subjects to return for all required follow-up visits. The clinical study objectives will not be realized if a significant number of subjects are lost to follow-up or discontinued from further study participation.

5.4.9 Reinterventions

Reinterventions to the study device (GORE® Septal Occluder) will be reported on the Intervention CRF. If the GORE® Septal Occluder is removed as part of the reintervention, then the subject is discontinued from the study. If the GORE® Septal Occluder remains implanted, then the subject will continue to be enrolled and will complete study follow-up as prescribed.

5.4.10 Follow-up Visit Windows

The follow-up visits should be completed within an acceptable time frame and in accordance with the protocol defined visit windows. The follow-up intervals are calculated as calendar days from index procedure. The visit windows are calculated as +/- the number of calendar days.

30 Days	6 Months	12 Months	24 Months	36 Months
Day 30 +/- 14 days	Day 180 +/- 14 days	Day 365 +/- 60 days	Day 730 +/- 60 days	Day 1095 +/- 60 days

If the visit is not able to be completed during these windows the visit should be completed as soon as possible; however, it will be considered a protocol deviation and should be reported per local Institutional Review Board (IRB) policy. Visits performed outside the prescribed window will be reported as an Unscheduled visit.

5.5 Subject Withdrawal from the Clinical Study

A subject may withdraw from the clinical study 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 such suitable physician cannot be identified.

The Investigator may withdraw the subject from the clinical study 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 clinical study objectives may not be realized if a significant number of subjects are lost to follow-up. A subject may withdraw, or be withdrawn by the Investigator, if he or she is unable to continue participation in the study due to any condition unrelated to the study.

The Investigator or designee must complete the appropriate CRF (Study Completion/Discontinuation Form) documenting the subject's withdrawal or discontinuation from the clinical study. The subject will be considered withdrawn once the Sponsor receives the respective CRF.

At any time other than the immediate index procedure during the study where complications prevent retention of the GORE® Septal Occluder (i.e., embolization or other event requiring device removal), the subject will be discontinued from further study follow-up. All adverse events will be collected and reported in compliance with this protocol through the point of device removal. The Investigator or designee will complete the Study Completion/Discontinuation Form documenting the subject's discontinuation from the clinical study.

5.6 Subject Lost to Follow-Up

A subject will be considered lost to follow-up and terminated from the study once they have missed at least one follow-up visit or at the discretion of the Investigator or Sponsor, 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.

5.7 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 due to voluntary withdrawal, physician withdrawal, death or any other reason will be considered a withdrawal. Subjects will not be provided with any medical care by the Sponsor after study completion or withdrawal.

5.8 Explant Procedures

The GORE® Septal Occluder may be explanted during a surgical procedure or as part of an autopsy. Investigative Centers are requested to return explanted device to W. L. Gore & Associates, Inc. for gross and histological evaluation. Prior to planned or potential device retrieval, contact the GORE® Septal Occluder Study Manager to communicate that a specimen is being retrieved from a study subject. A specimen shipping kit will be sent immediately to the Investigative Center. The specimen kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

6.0 Clinical Study Administration

6.1 Training

Participating Investigators are required to complete device didactic and protocol training prior to first implant. The first study implant is observed by a Gore representative and is considered a clinical training case.

6.2 Device Accountability and Storage

The GORE® Septal Occluder may be used only under the supervision of the Investigator and in strict accordance with this protocol and applicable laws and regulations. The occluder may be implanted only in subjects who meet the inclusion/exclusion criteria set forth in this protocol. The Investigator will maintain accurate, detailed records of all devices received from Sponsor. The Investigator will record and maintain records of each device used on the corresponding CRF, and will notify Sponsor immediately if any devices are damaged or unaccounted for. The devices must be accessible only to the personnel involved in the study and stored in a secure facility.

Upon completion or termination of the clinical study or the Investigator's participation in the clinical study, 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.

6.3 Core Laboratory

All protocol prescribed imaging (screening/pre-procedure, procedure, pre-discharge, 30 days, and 6, 12 and 36 months) must be recorded in DICOM format, subject information de-identified by turning off the system overlay feature and replaced with study ID, and images uploaded to BioClinica WebSend secure web portal. The Core Laboratory will access images through the BioClinica web portal and evaluate prescribed intervals. Results of core lab evaluations will be available on the subject EDC records.

6.4 Study Monitoring

Clinical Investigative Site monitoring for this study will be provided by Theorem Clinical Research. Monitoring oversight will be provided by the Sponsor.

The Investigative Site monitors are qualified by training and experience to oversee the progress of the study at the site and will ensure 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.

6.4.1 Monitoring Procedures

6.4.1.1 Clinical Investigative Site Initiation Visit

Site initiation will be performed to assure 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.

6.4.1.2 Periodic Clinical Investigative Site Visits

Periodic site visits will occur as necessary to ensure continuing adequacy of facilities and adherence to the clinical study protocol, the GCPs, and applicable regulations and laws that pertain to the conduct of the clinical study. During these visits, the 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.

6.4.1.3 Clinical Monitor Reports

The Sponsor's Clinical Monitor(s) 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 correctional action recommended, and any other information deemed pertinent by the Sponsor's Clinical Monitor.

6.5 Protocol Deviations

A protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and that has not been approved by the IRB. The Investigator is responsible for reporting protocol deviations to their IRB per IRB policy and the Sponsor promptly. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety and determine if additional reports or actions are required. Additional action may include site retraining, removal of devices from the site, and/or site termination.

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(s) to a subject.

6.6 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 ensure proper training of Investigator and site staff on all protocol amendments as necessary.

6.7 Sponsor Representatives

Sponsor representatives may be present during study procedures to support the Investigator. The representatives may provide guidance for use of the device.

6.8 Source Documents and Access to Source Data

The Investigator will keep all study records, source data and investigational devices available for inspection by the Sponsor, Sponsor's monitors, and regulatory authorities.

Source data is defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation.

6.9 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 study and for a minimum of two years after the latter of the date on which the study is terminated or completed, or the date the records are no longer required to support regulatory approval of the device. In any event, clinical study records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but are not limited to:

- All study-related correspondence with another Investigator, the IRB, the Sponsor, a Monitor, regulatory authority, or a study subject.
- Accountability records of receipt, use and disposition of all investigational devices including the type and quantity of the devices, the dates of their receipt, and the lot numbers. In addition, the names of all persons who received, used or disposed of each device.
- Subject records that include the subject's case history (e.g., medical records, reports of procedures, diagnostic tests and laboratory reports), the signed informed consent and process, and exposure to the device. In addition, all relevant observations, including records concerning adverse device effects, information and data on the condition of each subject upon entering and during the course of the investigation, and previous medical history should be retained. Pertinent information will be documented on standardized CRFs provided by the Sponsor.
- A copy of the study protocol and all amendments. Any deviations from the protocol will be documented.
- Reports and information pertaining to Unanticipated Adverse Device Effects (UADEs).
- All information pertaining to IRB review and approval of the clinical study. This includes a copy of the IRB approval or any subsequent renewal, the IRB-approved Informed Consent Form(s), and a certification stating that the IRB is in compliance with Food and Drug Administration (FDA) regulations.
- An original signed Investigator Agreement or equivalent.

The Investigator will prepare and submit the following reports:

- IRB approval withdrawal: information pertaining to withdrawal of IRB approval will be provided to the Sponsor within five 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 to the institutional IRB and to the Sponsor summarizing the Investigator's experience during the study.

Other:

- Any other reports as reasonably requested by the Sponsor or required by FDA.

6.10 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 study 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 study 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 study. 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.

7.0 Data Collection and Submission

The Clinical Data Management System (CDMS) for this study will be provided by Medidata Solutions Worldwide, 79 Fifth Avenue, 8th Floor, New York, New York 10003.

7.1 Data Collection Methods

This study will report clinical data using the Medidata Rave® web-based application. The Rave® system will be the database of record for the protocol

and subject to regulatory inspections. All Rave® users will be trained to use the CDMS and will comply with study specific guidelines/instructions.

Subject data will be collected using protocol-specific electronic case report forms (eCRF). eCRF Guidelines will be provided to sites at the time of database training. Site staff will enter data directly into the eCRF for review by the Sponsor and/or CRO.

7.2 Data Clarification and Correction

Once entered, data will be evaluated to ensure that it is complete, consistent and logically sound. Data changes or query resolution within the CDMS will be addressed at the site level. All changes, reasons for changes, and persons making the changes will be captured in the system's audit trail.

7.3 CRF Completion Schedule

All CRFs should be completed within 14 working days of each visit.

8.0 Risk Assessment

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

Some risks are possible with transcatheter approaches, including:

- access site complications
- incomplete closure of the defect
- repeat procedure to the septal defect
- 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® Septal Occluder device include, but are not limited to:

- unsuccessful device delivery

- fracture of the wire frame resulting in device instability or other clinical sequelae
- occluder disc expansion resulting in clinical sequelae or intervention
- possible allergic reaction to nickel in wires
- perforation of cardiac tissue by the device
- enlargement of the defect during or after device deployment
- embolization of the implant
- surgical intervention to correct device failure
- insufficient closure of the defect

8.1 Minimization of Risks

Potential risks associated with the use of the GORE® Septal Occluder will be minimized by the following:

- W. L. Gore & Associates, Inc. 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 the design of the occluder, its application, and preliminary clinical results from any pre-clinical and clinical studies.
- The site Investigator, Co- and/or Sub-Investigators, clinical study coordinator(s) or designee at each participating site will be trained to the protocol, reminded of the importance of patient selection and specific anatomy criteria when using the occluder, and subject follow-up requirements.
- Protocol inclusion/exclusion criteria and follow-up schedule were 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 adverse events.
- Data completed by the clinical sites will be monitored. An initiation site visit and interim site visit(s) will be conducted as appropriate to evaluate protocol compliance and to evaluate the data for accuracy and subject safety.
- Safety and efficacy data obtained during the clinical study 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 defect and anatomy is appropriate. Procedural echocardiographic or other appropriate imaging will be used to assess the subject defect suitability.
- Antiplatelet therapy will be prescribed for 6 months post index procedure to reduce the risk of thrombosis. Peri-procedural antibiotics prophylaxis is recommended to reduce the risk of infection.
- All protocol defined echocardiographic images will be reviewed by the Echocardiography 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 occluder size selected for the defect is recommended to be approximately 1.75:1 (device nominal diameter-to-defect diameter) and defects not greater than 17mm will be treated 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.

8.2 Summary of Expected Benefits

The expected benefit to the patient from the use of the GORE® Septal 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.

9.0 Adverse Events and Safety Monitoring

An adverse event (AE) is defined as any untoward medical occurrence in a subject whether device 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 UADE (see

section below), 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 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is defined 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 application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR Part 812.3).

"An Investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect" (21 CFR Part 812.150). 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 will be uploaded into the CDMS 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 effect.

9.3 Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its suspected relationship to the occluder device, interventional procedure, and/or study medications. Each relationship will be defined as either: definitely related, probably related, possibly related, unrelated, or unknown.

9.4 Serious Adverse Events

Each AE will be assessed by the Investigator for seriousness. Each AE is categorized as either Serious or Non-Serious. A Serious Adverse Event (SAE) is an adverse event that:

1. led to a death;
2. led to a serious deterioration in health of a subject that:
   - results in a life threatening illness or injury;
   - results in a permanent impairment of a body structure or body function;

- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; or

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

9.5 Adverse Event Severity

Each AE will be assessed by the Investigator for severity. The severity describes the maximum intensity of the adverse event; for purposes of consistency, these intensity grades are defined as follows:

Mild	Does not interfere with subject's usual function
Moderate	Interferes to some extent with subject's usual function
Severe	Interferes significantly with subject's usual function

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for seriousness, as described in section 9.4.

9.6 Adverse Event Data Collection

All study AEs will be collected, recorded on the appropriate CRF, maintained in the CDMS, and documented in the subject's permanent medical record.

Adverse event reporting requirements are as follows:

- Adverse Event Name
- Adverse Event Onset Date
- Severity (see Section 9.5)
- Primary Relationship (see Section 9.3)
- Seriousness (see Section 9.4)
- Treatment
- Action Taken
- Outcome
- Adverse Event Resolution Date
- If applicable, was AE cause of death.

Adverse Event Submission Guidelines:

- Adverse event reporting begins once the patient is enrolled in the trial. All adverse events should be reported from enrollment through study completion/discontinuation.
- An adverse event that changes from non-serious to serious should be reported as a new adverse event.
- Adverse events with an outcome status of "Ongoing" should be assessed at each follow-up evaluation to determine if the event

has resolved. Adverse events ongoing at study completion/discontinuation should be left as "Ongoing" on the AE case report form.

- Provide a diagnosis if possible. If unable to provide diagnosis, report the symptoms as separate events. Adverse Events should be reported without abbreviations or narratives.
- If a subject dies while on study, the cause of death will be reported as the adverse event and "death" reported as the event outcome on the AE case report form. If the subject has other ongoing adverse events at the time of death, the outcome status of those events should be reported as "death" on each AE case report form.

9.7 Adverse Event Coding

Adverse Events will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA) coding guidelines.

9.8 Independent Data Review

The Sponsor will establish an Independent Data Reviewer (IDR). The IDR will provide external oversight and review for potential safety concerns. The IDR is a physician expert in interventional cardiac therapy who is not participating in the trial and has no other affiliation with W. L. Gore & Associates, Inc.

During the course of the study, the IDR will review aggregate accumulating safety data to monitor for the incidence of serious adverse events and other trends that would warrant modification or termination of the study.

The IDR will review the overall safety data at regular intervals. The IDR responsibilities and operating procedures will be outlined in the IDR charter.

Any IDR 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 IDR at any time determines that a potential serious risk exists to subjects in the study, the IDR will immediately notify the Sponsor.

10.0 Statistical Analysis

10.1 Primary Study Hypotheses

This study is designed to test the null hypothesis that the Clinical Success rate at 6 months when using the GORE® Septal Occluder is inferior to the

Clinical Success rate at 6 months when using the GORE® HELEX® Septal Occluder device; versus the alternative hypothesis that the Clinical Success rate at 6 months when using the GORE® Septal Occluder is not inferior to the Clinical Success rate at 6 months when using the GORE® HELEX® Septal Occluder device.

The hypotheses are specified as follows:

$$H_0 : P_C - P_T \geq \Delta$$
$$H_A : P_C - P_T < \Delta$$

where:
P_C = the Clinical Success rate at 6 months when using the GORE® HELEX Septal Occluder (control arm)
P_T = the Clinical Success rate at 6 months when using the GORE® Septal Occluder (test arm)
Δ = the non-inferiority margin

10.2 Sample Size Assumptions

The safety and efficacy of the GORE® Septal Occluder will be evaluated by comparing this device to the currently marketed GORE® HELEX® Septal Occluder. To develop a control population for comparison to the GORE® Septal Occluder, an analysis of previous GORE® HELEX® Septal Occluder clinical studies was evaluated. The studies utilized included the HELEX® Device Continued Access Study (HLX 03-01) and HELEX® Device Post Approval Study (PAS HLX 06-04) as these were studies of the currently marketed implantable portion of the HELEX device (subsequent modifications to the delivery system have been made). The subject population in the HELEX device studies was limited to those subjects who would satisfy the defect size criteria for this study, specifically with defects ≤17 mm.

Table 10.2.1 presents the outcomes from the analysis of the HELEX device studies. Using the primary endpoint definition described in Section 3.2.3, the composite Clinical Success rate in the HELEX device studies was 86.6%.

Table 10.2.1
Composite Clinical Success with the GORE® HELEX Septal Occluder
GORE® HELEX Device Continued Access and Post-Approval Studies

	GORE® HELEX Septal Occluder
Subjects with Deployment Attempt[1]	
	[redacted]
Procedure Technical Success	
Implant Successful	[redacted]
Implant Unsuccessful	[redacted]
	[redacted]

Safety Outcomes at 6 Months	[redacted]
Serious AE: Day 0-30	[redacted]
Device Embolization	[redacted]
Device Removal	[redacted]
Other ASD Reintervention	[redacted]
Other Serious Adverse Event	[redacted]
Device Embolization: Day 31-182	[redacted]
Device Removal: Day 31-182	[redacted]
Other ASD Reintervention: Day 31-182	[redacted]
Overall	[redacted]
	[redacted]
Defect Closure Status at 6 Months (Core Lab)	
Occluded	[redacted]
Clinically Insignificant	[redacted]
Clinically Significant	[redacted]
Not Completed	[redacted]
Composite Clinical Success at 6 Months	
Success	[redacted]
Failure	[redacted]
Not Evaluated	[redacted]

[redacted]

10.3 Non-Inferiority Margin

The 6-month composite Clinical Success rate for the GORE® Septal Occluder will be considered non-inferior to the 6-month composite Clinical Success rate for the GORE® HELEX® Septal Occluder if the difference in rates ($P_C - P_T$) is less than 10%. This non-inferiority margin is based on (1) the 95% confidence interval lower bound for the estimated 6-month composite Clinical Success rate for the HELEX device (82%) and(2) a worst-case analysis of the 6-month composite Clinical Success rate for the HELEX device (81%, assuming the 18 subjects with missing echo evaluations were failures).

10.4 Sample Size Determination

Sample size for the Test group was estimated with Power and Sample Size (PASS) 2008 (Kaysville, UT) using a two-sample, non-inferiority binomial proportions test with the following assumptions:

Type I error (alpha)	0.05
1-Type II error (power)	≥0.86
N_C (HELEX sample size)	253
P_C (HELEX)	86.6%
P_T (GSO)	86.6%
Non-Inferiority margin	10%

Based on these conditions, it was estimated that 135 subjects with primary endpoint data will be required. To allow for an anticipated withdrawal and

lost to follow-up rate of up to 10% before the 6-month endpoint, a minimum of 150 subjects will be enrolled in the study.

10.5 Study Enrollment

Enrollment in the GORE® Septal Occluder study will occur in three phases:

1. Pivotal cohort of 50 subjects from a maximum of 10 sites. Enrollment in this phase will begin upon Investigational Device Exemption (IDE) approval. Upon completion of 6 month follow up for all 50 subjects, a submission will be made to FDA for Pre-Market Approval (PMA).
2. Continued Access cohort of 100 – 350 subjects from 10 – 21 (up to 11 additional) sites. Enrollment in this phase will begin after FDA acceptance of 30-day safety analysis on the Pivotal cohort.
3. Post Approval cohort of subjects will be enrolled depending on the number achieved in Continued Access upon PMA approval. Enrollment in this phase will begin after FDA pre-market approval for GORE® Septal Occluder. (Post Approval Study [PAS] subjects will be enrolled pursuant to the approval of this protocol and PMA.)

Total enrollment for the GORE® Septal Occluder study will be 150 – 400 subjects. All subjects will be enrolled and followed under the same criteria through the 36 months post index procedure.

10.6 Data Analysis

10.6.1 Timing of Analyses

There are three planned analyses for the GORE® Septal Occluder study:

1. A safety analysis on the pivotal cohort of 50 subjects at completion of 30 day Screening follow-up. This analysis will support expansion of enrollment into the continued access phase. This will be a descriptive analysis with no hypothesis testing.
2. A PMA submission analysis on the pivotal cohort of 50 subjects at completion of 6-month follow-up. This analysis will support pre-market approval of the GORE® Septal Occluder. This will be a descriptive analysis with no hypothesis testing.
3. The final study analysis at completion of enrollment of all subjects and completion of 36-month (3-year) follow-up. This analysis will evaluate the primary study hypothesis.

10.6.2 Analysis Populations

The analysis populations for the study are:

- Per-Protocol (primary analysis population) – this population will include enrolled subjects who had no inclusion/exclusion

violations and who complete evaluation through the 6-month follow-up.
- Intent-to-treat – this population will include all enrolled subjects.

10.6.3 Statistical Analysis of Primary Endpoint

The primary endpoint analysis will be a comparison of the proportion of subjects who meet the composite Clinical Success requirements through the 6-month follow-up between the study population and the historical control population of GORE® HELEX Septal Occluder studies. The primary analysis population will be the per-protocol population. The primary endpoint will be compared using a two-sample binomial proportions test with a non-inferiority margin of 10%. In statistical terms:

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

where:
p_C = observed Clinical Success proportion at 6 months in control group
n_C = number of subjects with primary endpoint evaluation in control group
p_T = observed Clinical Success proportion at 6 months in test group
n_T = number of subjects with primary endpoint evaluation in test group

The test statistic z is assumed to have a standard Normal distribution. Based on the alpha ≤0.05 criterion, a result of z< -1.64 will result in rejection of the null hypothesis in favor of the alternative hypothesis and a conclusion that the GORE® Septal Occluder is not inferior to the current GORE® HELEX Septal Occluder.

10.6.4 Statistical Analysis of Secondary Endpoints

The study is not designed to evaluate statistical hypotheses for the secondary endpoints. Therefore, no analyses are planned for the secondary endpoints. Any analyses would be considered exploratory. Secondary endpoints will be presented as descriptive statistics.

10.6.5 Evaluation of Poolability of Presence vs. Absence of Atrial Septal Aneurysm

Although the fraction of subjects enrolled with an atrial septal aneurysm (ASA) is expected to be small (perhaps 1 in 10) it is an important characteristic of ASD, and thus as a regulatory requirement will be

assessed for poolability with data from subjects without ASA. The statistical plan for this assessment will consist of two stages: baseline homogeneity and primary outcome comparability.

For baseline homogeneity, the two subgroups will be compared on the following three baseline demographic and predictor covariates: age, gender, and balloon-sized ASD diameter. These subgroup comparisons will use the two-sample t-test, chi-square test, or Fisher's Exact test, depending on the distribution of the covariate.

For primary outcome comparability, covariate-by-ASA interactions will be assessed using logistic regression models where main effects for ASA and the covariate and the covariate-by-ASA interaction term will be regressed on the 6-month Clinical Success endpoint; this will be performed individually for each of the three baseline covariates. Statistically significant interactions will be assessed graphically for the nature of the interaction (quantitative vs. qualitative). Qualitative interactions (difference in direction of ASA effect across levels of covariate) will suggest that the ASA subgroups are not poolable, leading to analyses performed separately for each ASA subgroup.

Finally, ASA subgroup and any baseline covariates deemed to be different between ASA subgroups will be included as main effects in a logistic regression model on the primary endpoint. If the ASA subgroup term is statistically significant then the ASA subgroups will not be considered outcome comparable, leading to analyses performed separately for each ASA subgroup.

A significance level of α=0.15 will be used for these poolability tests, without correction for multiplicity. Since this evaluation plan calls for a minimum of 7 significance tests, the overall Type-I error rate for this analysis may exceed $1 - (1 - 0.15)^7 = 0.67$.

11.0 Ethical and Regulatory Considerations

11.1 Statement of Compliance

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH_GCP), and applicable regulatory requirements.

21 CRF Part 11	Electronic Records; Electronic Signatures
21 CRF Part 50	Protection of Human Subjects
21 CRF Part 54	Financial Disclosure by Clinical Investigators
21 CRF Part 56	Institutional Review Boards
21 CRF 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 study 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 study. The Sponsor will ensure proper monitoring of the clinical study and ensure the Clinical Investigative Site has obtained Institutional Review Board (IRB) approval prior to enrollment. The Sponsor will provide information to the Investigators, the IRB, and the FDA concerning the progress and any new materials information about the clinical study.

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

11.3 Subject Informed Consent

The Investigator shall ensure that all potential subjects for this study are provided with a consent form describing this study 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 or designee before that subject undergoes any study procedure. The consent form will be signed and personally dated by the subject or legally acceptable surrogate, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the subject records. A copy of the informed consent document will be given to the subject for their records. Any significant, new information that emerges while the study is in progress that may influence a subject's willingness to continue to take part in the study will be provided.

The Investigator shall ensure that documentation of the acquisition of informed consent is recorded in each subject's records in accordance with 21 CRF 812.140.

11.4 Independent Ethical Review

The Investigator shall not enroll any subjects prior to obtaining approval for the study from a properly constituted Institutional Review Board.

The Investigator will submit the protocol, informed consent forms and other information to be provided to subjects, such as survey instruments or questionnaires, and any proposed advertising/recruitment materials for written approval prior to site initiation.

11.5 Conflict of Interest

All Investigators will follow their institution's conflict of interest policies.

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

11.6 Confidentiality

All subject records will be kept confidential to the extent provided by applicable laws and regulations. The study 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 independent ethical review board and other regulatory bodies (e.g. FDA).

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

12.0 References

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