GORE HELEX SEPTAL OCCLUDER

FDA Scientific Advisory Panel

Atrial Septal Defect Occluders Safety & Effectiveness

W.L. Gore & Associates, Inc. Panel Pack

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GORE

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I. EXECUTIVE SUMMARY

A. Background

Atrial septal defects ("ASDs") represent one of the most common forms of congenital heart disease. An ASD is an anomalous communication between the left and right atria, and, left untreated, may result in pulmonary hypertension, cardiomegaly, dyspnea upon exertion, right sided heart failure, and arrhythmia.[1] ASDs may occur anywhere on the atrial septum, however the most common form is *ostium secundum* ASD, representing up to 75% of all ASD.[2]

Treatment of hemodynamically significant ASDs is medically necessary. Current ACC/AHA guidelines for pediatric and adult congenital heart disease provide a Level Ib recommendation (evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective) for the surgical or transcatheter treatment of hemodynamically significant ASD, provided that anatomical considerations are suitable for device placement.[3,4] In the current era, patients with suitable anatomical features have either a surgical or transcatheter option for defect repair.

Surgical closure of *ostium secundum* ASD requires open heart surgery to close the defect with a patch. Surgical closure of ASD has been successfully performed for over 50 years and continues to be a safe and effective procedure; reliably closing the defect regardless of morphology or patient size while having a low rate of associated morbidity and mortality. Over the last few decades, transcatheter repair has arisen as an alternative treatment option for *ostium secundum* ASD. This minimally invasive alternative allows the patient to avoid the trauma and scarring associated with open heart surgery, while additionally providing an effective means for defect repair.

Currently, three devices are available for the transcatheter repair of atrial septal defects. These include the GORE® HELEX® Septal Occluder, the St. Jude AMPLATZER® Cribriform Occluder, and the St. Jude AMPLATZER® Septal Occluder. The GORE® HELEX® Septal Occluder's material, design, and mechanism of closure differ from that of the AMPLATZER® Occluders. Accordingly, their respective safety and effectiveness profiles are also different, giving rise to different adverse event types and rates.

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[1] Fleming GA, Doyle T, Graham TP Jr. Natural and unnatural history of a secundum ASD. In: Hijazi ZM, Feldman T, Sievert H, Al-Qbandi MHA, eds. *Transcatheter Closure of ASDs and PFOs: A Comprehensive Assessment.* 1st ed. Minneapolis, MN: Cardiotext Publishing; 2010;(2):17-26.
[2] Alkashkari W, Hijazi ZM. ASDs: clinical perspectives. In: Hijazi ZM, Feldman T, Sievert H, Al-Qbandi MHA, eds. *Transcatheter Closure of ASDs and PFOs: A Comprehensive Assessment.* 1st ed. Minneapolis, MN: Cardiotext Publishing; 2010;(3):27-36.
[3] Feltes TF, Bacha E, Beekman RH 3rd, *et al*; on behalf of the American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, and Council on Cardiovascular Radiology and Intervention. Indications for cardiac catheterization and intervention in pediatric cardiac disease: a scientific statement from the American Heart Association. *Circulation* 2011;123(22):2607-2652.
[4] Warnes CA, Williams RG, Bashore TM, *et al.* ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). *Circulation* 2008;118(23):e714-e833.

To gain approval for commercial use, the safety and efficacy of both the GORE® HELEX® Septal Occluder was compared to that of surgical closure within FDA-regulated clinical studies. Within the GORE® HELEX® Septal Occluder studies, a high rate of treatment success, a low rate of adverse events, and a shortened hospital stay were noted. Assessment of these data led to FDA approval of the device in 2006 as a safe and effective treatment option for *ostium secundum* ASD, providing yet another option for patients and physicians.

Transcatheter ASD closure remains a safe and effective alternative to surgical closure for appropriate defects in both shorter and longer term follow-up. This document presents data for the GORE® HELEX® Septal Occluder from two distinct sources, worldwide commercial experience dating back to 1999 and four multicenter IDE and Post-Approval Studies in the United States. These data demonstrate that the GORE® HELEX® Septal Occluder is effective at closing ASDs and that the adverse event rate experienced by patients is low, predictable, and stable over time.

B. GORE® HELEX® Septal Occluder

The GORE® HELEX® Septal Occluder was approved in the US in August, 2006, with the following indication:

The GORE® HELEX® Septal Occluder is a permanently implanted prosthesis indicated for the percutaneous, transcatheter closure of *ostium secundum* atrial septal defects (ASDs).

The discs of the GORE® HELEX® Septal Occluder are soft and conformable, comprised of a single helical wire substantially covered in biologically inert expanded polytetrafluoroethylene (ePTFE), as reflected in
Figure 1**.** This material allows for tissue ingrowth, which assists with defect closure.

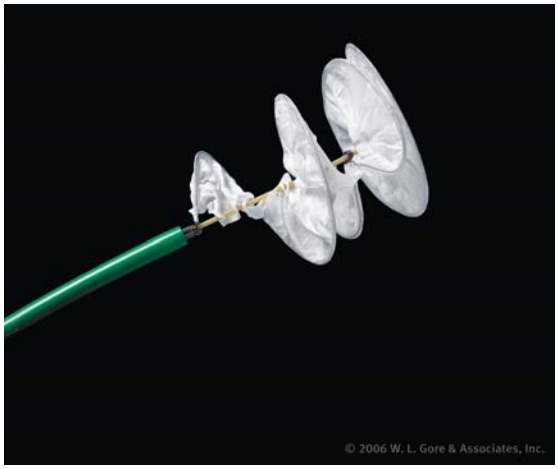

Figure 1. GORE® HELEX® Septal Occluder

A detailed device description is included in **Section II**, including the implantable **occluder** portion of the device, device **indications**, and a summary of device **modifications**, which have primarily been limited to delivery system changes. The modifications to the delivery system have improved ease of use for clinicians without impacting the device's safety and effectiveness for patients. The design of the implanted product has remained substantially unchanged through its 12-year clinical history, thus aiding in the comparison of clinical and commercial data presented herein.

C. Definitions of Major Safety Events of Interest

FDA has stated that the agency's key adverse events concerns regarding transcatheter repair devices are: erosions, device embolizations, wire frame fractures, thrombus, and arrhythmia. These adverse events are defined as follows:

Erosion: A device-anatomy interaction that causes a breakdown of the atrial wall resulting in hemodynamic compromise. This is a potentially emergent and life-threatening adverse event requiring reintervention. Procedural perforations, in general, are not caused by the device itself and are not considered erosions.

Device Embolization: Dislodgement of the occluder from the septum after conclusion of the procedure, and subsequent device migration to the pulmonary or systemic circulation. This event may lead to either transcatheter or surgical reintervention to retrieve the device.

Wire Frame Fracture: One or more fractures of the wire frame of the device. This event seldom requires treatment. However, instances which adversely impact the stability of the device or impact adjacent cardiac structures may lead to transcatheter or surgical reintervention.

Arrhythmia: Irregular or loss of heart rhythm. This event may lead to medical or transcatheter or surgical reintervention.

Thrombus: Thrombus formation is the procedural or post-procedural identification of an echogenic mass or thrombus on the occluder. This event may lead to medical, transcatheter, or surgical reintervention.

Other Adverse Events Requiring Surgical/Transcatheter Reintervention: In addition to the events above, other adverse events may occur that require reintervention to the device and/or defect. As these events represent a potential safety risk to the patient, they are also considered in this report.

Adverse events have been evaluated in the context of the GORE® HELEX® Septal Occluder clinical studies and worldwide commercial device use.

D. GORE® HELEX® Septal Occluder Clinical Experience

1. Data Sources of Commercial Experience and US Clinical Studies

The GORE® HELEX® Septal Occluder device performance is drawn from two distinct sources: 1) Multicenter IDE and Post-Approval Clinical Studies for the ASD indication conducted in the US beginning in 2000, and 2) Commercial distribution beginning in 1999 outside the United States (OUS) and in the United States after PMA approval in August 2006 for ASD and all-use applications[5]. The post approval clinical study remains underway, and is expected to be completed in 2014. Together, these sources represent more than 1000 patient-years of follow-up data within clinical studies, and more than 12 years of commercial experience with the device. Data from these studies are detailed in **Section III: ASD Clinical Experience**. A high level summary of this information follows.

2. Clinical Study Experience

Gore has completed 3 prospective, multicenter clinical studies of the GORE® HELEX® Septal Occluder (Feasibility, Pivotal, and Continued Access) and has a fourth study in progress (Post Approval Study). These studies, combined, have enrolled 435 subjects and include more than 1000 patient-years of follow-up for the GORE® HELEX® Septal Occluder. In addition, the Pivotal Study included a surgical control arm, results of which are reported in **Section III: ASD Clinical Experience**.

a. Defect Closure – Clinical Study Experience

Combined data on ASD closure in clinical trial subjects receiving the GORE® HELEX® Septal Occluder, as evaluated by an independent echocardiography core lab, are provided in **Table 1.**

Table 1. Combined GORE® HELEX® Septal Occluder Clinical Studies Residual Defect Status: Echo Core Lab Review

Subjects Retaining Device (N=435)	12 Months	36 Months	60 Months
Subjects with Core Lab Review	356	127	87
Clinically Successful Closure	350 (98.3%)	126 (99.2%)	87 (100%)
Clinically Significant Leak	6 (1.7%)	1 (0.8%)	0 (0.0%)

Note: Month 12 follow-up window extended through Day 548, Month 36 follow-up extended through 1276, Month 60 follow-up extended through Day 2006.

Clinically successful closure was attained in greater than 98% of patients at all time points. No interventions due to significant leaks were noted within this population. Additionally, of the evaluable patients that were evaluated by the core lab at the 60 month follow-up window, 100% had clinically successful closure.

[5] The GORE® HELEX® Septal Occluder is indicated for both *ostium secundum* and atrial septal defects in select markets outside the US. Additionally, the device is currently being investigated for the prevention of recurrent stroke in patients with cryptogenic stroke and a PFO.

b. Safety Information – Clinical Study Experience

The incidence of adverse events of interest (erosions, device embolizations, wire frame fractures, thrombus, and arrhythmia), and the treatment chosen to resolve them, is reflected in **Table 2.** These data demonstrate that the adverse event rate experienced by patients is low, predictable, and stable over time. Most serious adverse events can be treated with minimally invasive techniques. In the event an open surgical repair is needed to treat an adverse event, such procedures have a long, reliable history in the repair of atrial septal defects and subsequent treatment is not impeded by the presence of the GORE® HELEX® Septal Occluder.

Table 2. GORE® HELEX® Septal Occluder Clinical Studies Adverse Events and Reported Treatments Number of Subjects by Adverse Event and Treatment Type

Subjects Receiving Device (N=435)	Events	Treatment for Event		
		Medical[1]	Transcatheter	Surgery
Patients requiring a medical, transcatheter, or surgical intervention	**18**	**2**	**8**	**8**
Erosion	0 (0.0%)	-	-	-
Device Embolization (post- procedure)	6 (1.4%)	-	5 (1.1%)	1 (0.2%)
Device removal due to fracture	5 (1.1%)	-	1 (0.2%)	4 (0.9%)
Arrhythmia	3 (0.7%)	2 (0.5%)	1 (0.2%)	-
Thrombus	0 (0.0%)	-	-	-
Other Adverse Events Requiring Intervention[2]	4 (0.9%)	-	1 (0.2%)	3 (0.7%)

[1] Includes cardioversion for arrhythmia
[2] Included device removal for sizing (n=2), malposition (n=1), and a potential nickel allergy (n=1).

c. Summary of US Clinical Study Experience

The GORE® HELEX® Septal Occluder clinical trial data support the positive risk/benefit profile associated with the device's use. Patients treated with the GORE® HELEX® Septal Occluder are able to avoid the trauma and scarring associated with open surgical repair, as well as the associated extended hospital stay. These patients experienced successful efficacy outcomes, i.e. the device effectively closed the defect.

With regard to identified risks, a small percentage of patients experienced major adverse events that required some form of reintervention (medical, transcatheter or surgical). Post-procedure device removal was required in 3.4% of clinical study patients, 40% of these were accomplished via a subsequent transcatheter procedure. The leading cause for device removal was device embolization, occurring in 1.4% of patients (all of which received an undersized device per Gore's current recommendations). Additionally, removals due to wire frame fractures occurred in 1.1% of patients due to septal apposition and/or device instability. These events do not preclude subsequent transcatheter or surgical repair of the defect. Of note, ***none of these events required an emergency conversion to surgery***.

The outcomes in the combined clinical studies highlight the following key findings:

- Of the evaluable patients that were evaluated by the core lab at the 60 month follow-up window, 100% had clinically successful closure.
- Clinical data indicate there is no difference in risk of major adverse event by age.
- No device or procedure-related deaths were reported in the clinical studies.
- Device embolization occurred in 1.4% (6) of patients. Most embolized devices were removed via a repeat transcatheter procedure. All device embolizations occurred in cases where the nominal device diameter was less than twice the balloon sized defect diameter. This information highlights the importance of adhering to the sizing recommendations, i.e. a 2:1 nominal device diameter to defect diameter ratio.
- Wire frame fractures occurred in 8.3% (26) of patients overall and rates for fracture were higher in larger devices. Wire frame fractures leading to device removal are not common; occurring in 1.1% (5) of subjects.
- Arrhythmia requiring treatment potentially related to the device and/or procedure is rare (<1%).
- No reports of device-related thrombus were observed acutely or in follow-up.
- No reports of erosions were observed acutely or in follow-up.
- No major adverse events were observed that required an emergency conversion to surgery.
- Current recommendations included in the device's *Instructions for Use* (IFU) are sufficient for minimizing the risks identified in the clinical study data.

The clinical data demonstrate the safety and effectiveness of the GORE® HELEX® Septal Occluder. The clinical studies served to outline the scope of potential major adverse events. Incidence rates of adverse events did not increase over time. These data confirm that the benefits of device use, according to its approved labeling, continue to outweigh observed risks of such use. These clinical data support the continued clinical use of the GORE® HELEX® Septal Occluder as a safe and effective treatment option for patients needing repair of *ostium secundum* ASD.

3. Post-FDA Approval ASD Commercial Experience (Worldwide)

a. Defect Closure – Post-FDA Approval ASD Closure Experience

Peer reviewed literature supports the efficacy of the GORE® HELEX® Septal Occluder for the occlusion of *ostium secundum* ASD (see **Section VI: Review of Published Literature**). Literature reports of ASD closure reaffirm Gore's clinical study findings of 98% clinically successful closure (see **Attachments 1** and **2)**. This appears to be corroborated by a review of worldwide adverse events, as reported in FDA's MAUDE (Manufacturer and User Facility Device Experience) database, which reveal a low rate of reintervention for residual leaks.

b. Safety Information – Post-FDA Approval ASD Closure Experience

It is estimated that 5,920 to 8,560 GORE® HELEX® Septal Occluder devices worldwide have been implanted in ASD patients since FDA approval of the device in August, 2006. The nature of adverse events, their frequency, and the subsequent treatment required are noted in **Table 3**.

As reported in the MAUDE database, adverse events are of the same type seen in clinical trials. With larger populations, events that occur at a very low frequency have become visible, but these events have continued to be reported at a very low rate. ***Of note, no late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention.***

Table 3. GORE® HELEX® Septal Occluder Post-FDA Approval Worldwide ASD Adverse Events and Reported Treatments

Commercial Implants (N = 5,920-8,560)	# of Events (lower%, upper%)	Treatment for Event				
		None	Medical[1]	Transcatheter	Surgery	Death
Patients requiring a medical, transcatheter, or surgical intervention	**89**	**2**	**7**	**41**	**38**	**1**
Erosion	0	0	0	0	0	0
Device Embolization (post-procedure)	34 (0.40%, 0.57%)	0	0	22	12	0
Leaks / Apposition[2]	31 (0.36%, 0.52%)	0	0	16	15	0
Frame Fractures[3]	13 (0.15%, 0.22%)	2	0	3	8	0
Arrhythmia	10 (0.12%, 0.17%)	0	5	3	2	0
Thrombus	3 (0.04%, 0.05%)	0	1	1	1	0
Other Adverse Events Requiring Intervention[4]	11 (0.13%, 0.19%)	0	0	2	8	1

[1] Includes cardioversion for arrhythmia.
[2] Apposition/Leak includes all reports of intervention for residual leaks and poor device apposition in the presence or absence of frame fractures.
[3] Unique events falling within the other category included entrapment, procedural effusions, post-procedural effusions, valvular damage, blood transfusion, access site complications, and surgical removal for unknown reasons. These events are detailed in **Section III**.
[4] Reasons for removal of fractured device included residual leak or poor apposition (n = 9, 3-transcatheter, 6-surgical) and valvular damage (n = 1, surgical).

Device embolization was noted as the most frequent adverse event, though it occurred very infrequently (0.40%-0.57%). During the clinical trials, embolization was found to be related to improper device sizing. Gore continues to emphasize the importance of device sizing in commercial physician training, labeling, and case support. Device embolization does not impede subsequent transcatheter or surgical repair.

A detailed description of all adverse events, the derivation of numerators and denominators, and resulting event rates are included within **Section III: ASD Clinical Experience**. Additionally, risk mitigators for adverse event are discussed in **Section V: Safety**.

c. Summary of Post-FDA Approval ASD Closure Experience

Post FDA Approval commercial ASD data from August, 2006 thru December, 2011, predict that <2% of patients will experience a reportable adverse event. In the commercial population, a repeat transcatheter procedure was required in <1% of patients. Additionally, a repeat surgical procedure was required in <1% of patients. These data are reflected in **Table 4**:

Table 4. Reported Treatment for Major Adverse Events, Worldwide ASD Patients

Patient Outcomes	ASD Implants		
	Lower Estimate (N=5,920)	Likely Estimate (N=7,240)	Higher Estimate (N=8,560)
No Adverse Event, or event managed via Medical Therapy Only	98.65%	98.90%	99.07%
Catheterization	0.69%	0.57%	0.48%
Access site procedure	0.03%	0.03%	0.02%
Surgery	0.61%	0.50%	0.42%
Death	0.02%	0.01%	0.01%

This commercial experience aligns with the experience of subjects in the clinical studies, where the sponsor and patients have the benefit of more robust follow-up.

Post FDA Approval, worldwide ASD commercial experience data continue to support the conclusion that the benefits associated with use of the GORE® HELEX® Septal Occluder outweigh the potential risks.

E. Risks and Benefits to Treatment using the GORE® HELEX® Septal Occluder in ASDs

The GORE® HELEX® Septal Occluder is an effective treatment option for patients with *ostium secundum* atrial septal defects. The adverse event rate experienced by patients is low, predictable, and stable over time. As with any major medical procedure, serious adverse events may occur. With this device, the most frequently encountered adverse events were post-procedural device embolization or reinterventions due to poor septal

apposition or residual leaks. Treatment of these adverse events includes either a repeat transcatheter or surgical intervention, however more than 99% of patients implanted with the device are able to avoid the potential trauma, tissue scarring, extended hospital stay and recovery associated with the open heart surgical alternative for treatment.

No late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention. Adverse events identified during post-market surveillance were consistent with those identified or anticipated in the clinical studies, and with those listed in the device's labeling as potential adverse events, as detailed in **Table 5**

Table 5. Comparison of Clinical Trial and Post FDA Approval ASD Experience Data

Subjects Retaining Device	Clinical Trial Data (N=435 patients)	Post FDA Approval ASD Commercial Experience (N=5,920 – 8,560 implants)	Complication Seen In Clinical Trial	Complication Noted in IFU
Estimated Major Adverse Event Rate	22 (5.1%)	89 (1.04% - 1.50%)	-	-
Apposition/Leak[1]	8 (1.8%)	31 (0.36% - 0.52%)	Yes	Yes
Embolization (post-procedure)	6 (1.4%)	34 (0.40% - 0.57%)	Yes	Yes
Fracture of device requiring removal	5 (1.1%)	11 (0.13% - 0.19%)	Yes	Yes
Arrhythmia requiring ongoing treatment	3 (0.7%)	10 (0.12% - 0.17%)	Yes	Yes
Valvular Damage	1 (0.2%)	2 (0.02% - 0.03%)	Yes	Yes
Access Site Bleed	1 (0.2%)	1 (0.01% - 0.02%)	Yes	Yes
Allergic reaction	1 (0.2%)	1 (0.01% - 0.02%)	Yes	Yes
Thrombus	0	3 (0.04% - 0.05%)	-	Yes
Peripheral vessel damage/surgery	0	3 (0.04% - 0.05%)	-	Yes
Effusion, or Tamponade (procedural)	0	3 (0.04% - 0.05%)	-	Yes
Effusion, post-procedural	0	2 (0.02% - 0.03%)	-	Yes
Entrapment	0	2 (0.02% - 0.03%)	-	Yes
Procedure-related Death[2]	0	1 (0.01% - 0.02%)	-	Yes
Surgical Removal (unknown cause)	0	1 (0.01% - 0.02%)	-	Yes
Erosions	0	0	-	Discussed as not occurring

[1] Apposition/Leak includes all reports of intervention for residual leaks and poor device apposition in the presence or absence of frame fractures.
[2] Procedural-related death involved a case with multiple interventions including the use of the GORE® HELEX® Septal Occluder

With larger populations, events that occur at a very low frequency have become visible, but these events have continued to be reported at a very low rate. Complications observed in the commercial experience align with the findings of the US clinical trials.

The clinical significance of post procedural adverse events experienced with the use of the GORE® HELEX® Septal Occluder range from medical management through an open surgical repair. The majority of adverse events, which occur in <2% of patients, are treated with a repeat transcatheter procedure. Less than 1% of patients require an open surgical repair as a result of a device related adverse event. More than 99% of patients treated with the device avoid the potential trauma, tissue scarring, extended hospital stay, and prolonged recovery associated with an open procedure. For the patients who require surgical reintervention, the use of the GORE® HELEX® Septal Occluder does not preclude such treatment. These patients may experience the range of complications reported in the peer-reviewed literature for open surgical repair of ASDs. The device remains a viable, safe, and effective treatment option for patients with *ostium secundum* ASD.

F. Conclusions

The GORE® HELEX® Septal Occluder is effective at closing atrial septal defects and the adverse event rate experienced by patients is low, predictable, and stable over time. With a high rate of clinical success, patients treated with the GORE® HELEX® Septal Occluder avoid the trauma and scarring associated with open surgical repair, as well as the extended hospital stay that surgical repair requires. Use of the GORE® HELEX® Septal Occluder does not create additional risk if reintervention is required.

The clinical studies and worldwide clinical experiences with the GORE® HELEX® Septal Occluder reflect the following:

- >98% of patients receiving the device achieve clinically successful occlusion of their defect by the 12 month follow-up.
- Clinical data indicate there is no difference in risk of major adverse event by age.
- ***No late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any device related events requiring late emergency device-related surgical intervention.***
- Nominal device diameter to defect diameter ratio (i.e., device sizing) is important for clinical success. The device may embolize if not correctly sized.
- Adverse events resulting from use of the GORE® HELEX® Septal Occluder are infrequent and well understood, and can be managed to provide clinical success for the patient.
- The majority of major adverse events encountered in conjunction with the use of the GORE® HELEX® Septal Occluder can be managed via a second catheterization procedure, especially so if the adverse event is identified early. Early discovery and identification can minimize the need for surgical intervention.

- Few new major occluder-related adverse events have appeared since the clinical trials, and all are appropriately documented in the device's *Instructions for Use.*
- When utilized according to its *Instructions for Use*, the GORE® HELEX® Septal Occluder offers a safe and effective treatment option for patients with *ostium secundum* atrial septal defects.

The data summarized in this document, and the changes made to the device over its history, reflect Gore's commitment to product stewardship. Gore's quality systems, including adverse event reporting, ensure that as understanding of device performance evolves, Gore makes timely modifications to the device, its labeling, or clinician training necessary to maintain the safe and effective use of the device.

Gore's data from both clinical studies and the world wide commercial experience reflect low, stable, and predictable adverse event rates for the GORE® HELEX® Septal Occluder used in ASD closure. These data predict that <2% of patients will experience an adverse event requiring intervention. This safety profile, coupled with the effectiveness of the device in closing the underlying defect, with minimal trauma and scarring, and allowing patients to promptly return to activities of daily living, demonstrate the safety and efficacy of the GORE® HELEX® Septal Occluder for patients.

Patients and their families tend to prefer transcatheter closure whenever possible. This motivation is fully supported by the clinical data underlying the safety and effectiveness of the GORE® HELEX® Septal Occluder. It is further driven by the desire of patients and families to receive successful treatment through a minimally invasive procedure. The clinical data on the GORE® HELEX® Septal Occluder continues to reflect its safe and effective clinical performance; and its clinical history reveals ***no late adverse events that cause hemodynamic compromise requiring emergency surgical intervention, i.e., erosions***, ***or any events requiring late emergency device-related surgical intervention***. Thus, the GORE® HELEX® Septal Occluder continues to provide patients a safe and effective treatment option that may be selected with the guidance of their treating clinician.

II. DEVICE DESCRIPTION

A. Device Description: GORE® HELEX® Septal Occluder

1. Indications for Use

The GORE® HELEX® Septal Occluder is a permanently implanted prosthesis indicated for the percutaneous, transcatheter closure of *ostium secundum* atrial septal defects (ASDs).

2. Technological Characteristics

The approved GORE® HELEX® Septal Occluder is comprised of an implantable prosthesis (occluder) and a catheter delivery system. The focus of this document is on the occluder portion of the device, described below. Additional detail on the delivery system is included in the *Instructions for Use* at **Attachment 3,** and the Clinician Training Manual at **Attachment 4**.

The GORE® HELEX® Septal Occluder implantable device is helical in shape when elongated and supported by the delivery system, but forms a low profile generally circular helical shape when fully deployed in the heart **(Figure 2**). The implantable device is comprised of a hydrophilic, ePTFE material supported by a single nickel-titanium (Nitinol) supporting wire frame and spaced by distal, center, and proximal Nitinol eyelets. The ePTFE material is bonded to the Nitinol support wire by a fluorinated ethylene propylene (FEP) coating.

The GORE® HELEX® Septal Occluder implantable device is supplied in five sizes sufficient to give the deployed right and left atrial discs nominal diameters of 15 mm, 20 mm, 25 mm, 30 mm, or 35 mm. The GORE® HELEX® Septal Occluder is deployed from a 10-French (Fr) outer diameter delivery system.

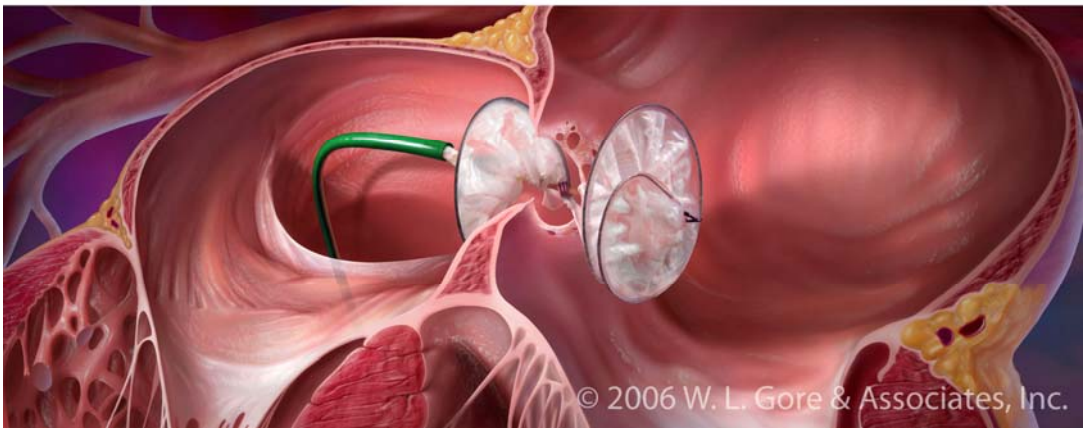

Figure 2. The GORE® HELEX® Septal Occluder

3. Principles of Operation

The GORE® HELEX® Septal Occluder functions by covering the defect and adjacent tissue with the inert ePTFE patch supported by the Nitinol wire frame.

Once the delivery system is located in the right atrium, the principal steps of the transcatheter procedure are the following:

- Position delivery catheter across the defect into the left atrium
- Deploy the left atrial disc
- Pull back on delivery system until the GORE® HELEX® Septal Occluder is in contact with septal wall
- Deploy the right atrial disc
- Set the lock on the GORE® HELEX® Septal Occluder
- Remove delivery system

These steps are depicted below in **Figure 3.** Following deployment, the GORE® HELEX® Septal Occluder remains in position across the defect with the aid of the lock loop and the blood pressure that pushes the ePTFE patch against the atrial septum.

When fully deployed, the left and right atrial discs of the GORE® HELEX® Septal Occluder bridge the septal defect to reduce or stop the shunting of blood between the left and right atria through tissue in-growth. The inert ePTFE patch is microporous and will become attached to the atrial septum by cellular penetration through the membrane micropores. Over time, the process of tissue attachment to the ePTFE patch will maintain the occluder in position and create a permanent defect closure.

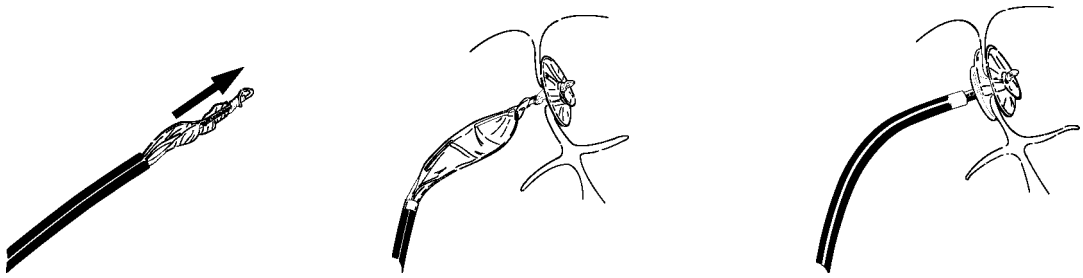

Figure 3. Illustration of GORE® HELEX® Septal Occluder Implant Procedure.

Deployment and operation instructions for the GORE® HELEX® Septal Occluder are included at **Attachment 3** ***Instructions for Use***. This document reflects Gore's current understanding regarding the best practices and expected outcomes associated with the use of the device. Further, a product animation clip illustrates the device principles of

operation for the device. This clip is included at **Attachment 5** on the CD that includes Attachments to this document.

B. Device Regulatory History

The GORE® HELEX® Septal Occluder was first used clinically in 1999 pursuant to its CE Mark. Thereafter, various changes to the device design have been incorporated based on clinician feedback and clinical data. These changes have largely been made to the delivery system of the device, whereas the occluder has remained unchanged since 2003. The following table illustrates the design changes that have been incorporated:

Table 6. Design Changes Implemented in Response to Clinician Feedback

Device Iteration	Description of Change	Reason for Change
Version 1.1 (circa 2003, in US; approved commercially in 2006)	***Occluder*** design change: Addition of hydrophilic coating to the ePTFE occlusion membrane Reversal of winding pattern of the wire frame	 Improve the ultrasound visibility of the occluder Improve the profile of the left atrial disc, once deployed
Version 1.5 (circa 2007, in US)	***Delivery system*** design change: Centralization of delivery system components Incorporation of distal guidewire port Inclusion of separate lumens to house retrieval cord Addition of control catheter tip slot	 Improve ease of use associated with device deployment Enable device to be delivered by monorail technique Prevention of retrieval cord entanglement Improve consistency of device locking
Version 2.0 (circa 2011, in US)	***Delivery system*** design change: Inclusion of stainless steel stiffener within mandrel Addition of hydrophilic lubricious coating to the control catheter Strengthening of retrieval cord	 Assist the prevention of mandrel kinking Decrease the deployment forces within delivery system Help prevent the occurrence of retrieval cord breaks

Relevant PMA Supplements approved since the approval of the Original PMA in August, 2006, are reflected in **Table 7.**

Table 7. PMA Supplement History

Supplement Number	Date Approved	Brief Description
P050006	08/11/06	Approval for the GORE® HELEX® Septal Occluder. The GORE® HELEX® Septal Occluder is a permanently implanted prosthesis indicated for the percutaneous, transcatheter closure of *ostium secundum* atrial septal defects (ASDs).
P050006/S001	09/21/07	PMA Supplement for design modifications for the catheter delivery system (HELEX® 1.5 delivery system).
P050006/S002	12/13/06	PMA Supplement for modification of the GORE® HELEX® Septal Occluder post approval study protocol; specifically, the analysis population.
P050006/S014	1/11/11	PMA Supplement to update the *Instructions for Use* (IFU)
P050006/S016	1/11/11	PMA Supplement approval to modify the GORE® HELEX® Septal Occluder delivery system which includes a lubricious coating applied to the control catheter, a stainless steel mandrel stiffener, and a stronger retrieval cord; these modifications are referred to as the 2.0 Delivery System Improvements.

III. ASD CLINICAL EXPERIENCE

The safety and efficacy of the GORE® HELEX® Septal Occluder is represented in this section which includes overviews of four clinical studies and the worldwide commercial experience. Major adverse events, and more specifically the adverse events of interest, are presented here within the context of the individual and combined clinical studies and commercial device reporting environments. An individual, detailed discussion of each adverse event of interest is presented in **Section V: Safety**.

A. Definitions of Major Safety Events of Interest

FDA has stated that the agency's key adverse events concerns regarding transcatheter repair devices are: erosions, device embolizations, wire frame fractures, thrombus, and arrhythmia. These adverse events are defined as follows:

Erosion: A device-anatomy interaction that causes a breakdown of the atrial wall resulting in hemodynamic compromise. This is a potentially emergent and life-threatening adverse event requiring reintervention. Procedural perforations, in general, are not caused by the device itself and are not considered erosions.

Device Embolization: Dislodgement of the occluder from the septum after conclusion of the procedure, and subsequent device migration to the pulmonary or systemic circulation. This event may lead to either transcatheter or surgical reintervention to retrieve the device.

Wire Frame Fracture: One or more fractures of the wire frame of the device. This event seldom requires treatment. However, instances which adversely impact the stability of the device or impact adjacent cardiac structures may lead to transcatheter or surgical reintervention.

Arrhythmia: Irregular or loss of heart rhythm. This event may lead to medical or transcatheter or surgical reintervention.

Thrombus: Thrombus formation is the procedural or post-procedural identification of an echogenic mass or thrombus on the occluder. This event may lead to medical, transcatheter, or surgical reintervention.

Other Adverse Events Requiring Surgical/Transcatheter Reintervention: In addition to the events above, other adverse events may occur that require reintervention to the device and/or defect. As these events represent a potential safety risk to the patient, they are also considered in this report.

Adverse events have been evaluated in the context of the GORE® HELEX® Septal Occluder clinical studies and worldwide commercial device use.

B. ASD Clinical Studies

1. Introduction

Starting in 2000, the GORE® HELEX® Septal Occluder has repeatedly demonstrated a strong safety profile across four prospective, multi-center, clinical studies for the treatment of *ostium secundum* ASD. These studies now include 435 subjects receiving the device with more than 1000 patient-years of follow-up. The following sections summarize the results of the individual studies. Additionally, the combined study data from the four trials are presented demonstrating the device's marked safety profile in the application of ASD closure. **Figure 4** highlights the chronology, the number of subjects, and the consented follow-up period of the 4 clinical studies.

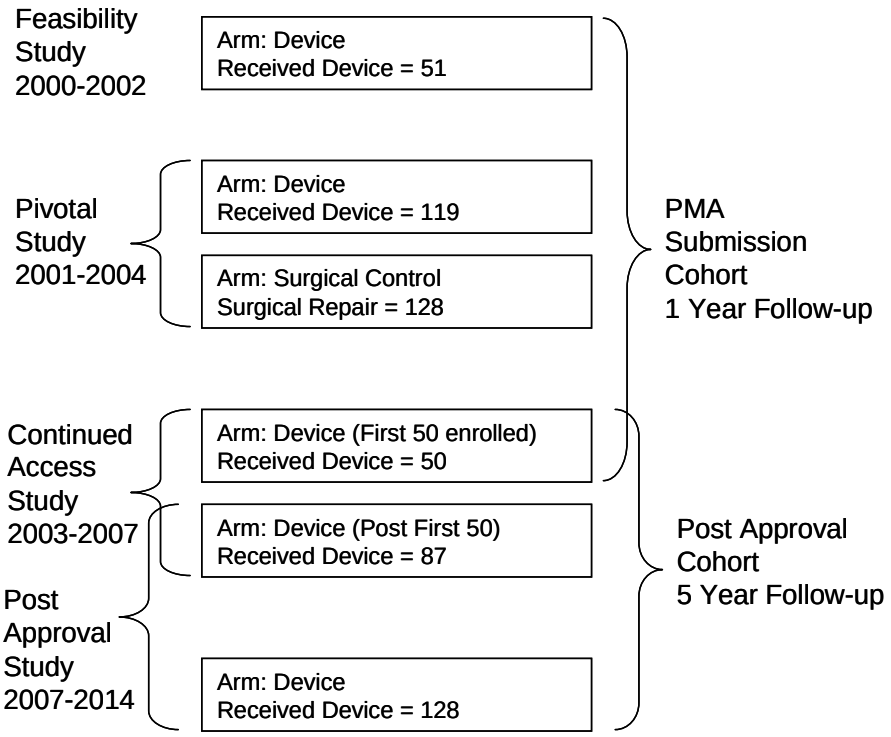

Figure 4. Clinical Studies of the GORE® HELEX® Septal Occluder

An independent Data and Safety Monitoring Board (DSMB) reviewed all reported adverse events throughout the course of the clinical studies. The DSMB is comprised of two cardiologists, two surgeons, and a biostatistician. The DSMB adjudicated each event to determine severity (major or minor) and relationship to device and/or procedure. The decision of the DSMB was considered final and their determinations were used in analyses of adverse events.

The GORE® HELEX® Septal Occluder clinical trial data support the positive risk/benefits profile associated with the device's use. The benefits of the device, used within the indications and approved labeling outweigh any known risks. Patients treated with the GORE® HELEX® Septal Occluder avoid the trauma and tissue scarring, and extended hospital stay associated with open surgical repair. These patients also had successful efficacy outcomes, i.e. the device effectively closed the defect. Adverse events requiring either surgical or interventional correction were rare.

2. Overview of Individual Clinical Studies

The following sections provide an overview of each clinical study and include:

- A summary of number of subjects, enrollment period, age of subjects, and follow-up period
- All reported major adverse events ("major" defined as requiring treatment/reintervention, or resulting in permanent deficit)
- All reported wire frame fracture events with or without subsequent device removals. Only wire frame fractures in the presence of conditions likely to result in a reintervention were considered major adverse events. The majority of wire frame fractures did not require reintervention to the device as the fracture did not affect the device's efficacy.
- Efficacy outcomes (clinically successful ASD closure) and composite clinical success endpoint (no major adverse event and clinically successful closure)
- Study conclusions

These sections are intended to focus on the events of interest for this panel review (erosion, device embolization, wire frame fracture, thrombus, stroke, and perforation) and only provide a high-level overview of other study characteristics/outcomes. The Multicenter Pivotal Study summary includes an overview of the surgical control arm data and conclusions from the comparison to the device arm data.

Additional information regarding the Feasibility, Pivotal, and Continued Access Studies is included in **Attachment 6: Summary of Safety and Effectiveness Data (SSED)** published by FDA in August, 2006 with approval of the GORE® HELEX® Septal Occluder PMA P050006, and in **Attachment 3: Instructions for Use** which was updated recently to include the complete Continued Access Study one-year follow-up data. Further details regarding each clinical study and definitions used for adverse events and ASD closure are provided in **Attachment 7: Expanded Clinical Trial Detail**. Also, Protocols and Final Reports of the studies are included at **Attachments 7.1-7.4**).

3. Feasibility Study

The objective of the **Feasibility Study** was to obtain an initial evaluation of the safety and performance of the GORE® HELEX® Septal Occluder for the closure of *ostium secundum* atrial septal defects. Fifty-one (51) subjects from two sites received the device in this study between April, 2000, and March, 2001. Median age was 11 years

and 70% of subjects were less than 21 years old. All subjects were followed for one year post procedure.

- One or more major adverse event was reported in 2 subjects (3.9%) through the 12-month follow-up, as presented in **Table 8.** A total of 2 major adverse events were reported in the 2 subjects. A summary of wire frame fractures is presented in **Table 9**.

  A note on presentation of adverse events in this report: Each cell of a table presents the number of subjects reporting a major adverse event for the row and column classifications. As a result, the column subtotals and row subtotals may not equal the overall row and column counts as a subject could report multiple occurrences of an adverse event type and/or can experience more than one major adverse event type in a given column interval.

Table 8. GORE® HELEX® Septal Occluder Feasibility Study Major Adverse Events Through 12-Month Follow-up Number of Subjects by Adverse Event Type and Timing of Onset

	Time Post-Procedure			
Subjects Receiving Device (N=51)	**Days 0-1**	**Days 2-30**	**Day 31 - Month 12**	**Overall**
Subjects Evaluable for Safety	51	51	50	51
Subjects With One or More Major Adverse Events	0 (0.0%)	0 (0.0%)	2 (4.0%)	2 (3.9%)
Arrhythmia	-	-	1 (2.0%)	1 (2.0%)
Seizure	-	-	1 (2.0%)	1 (2.0%)

Note: Month 12 follow-up window extended through Day 548.

Table 9. GORE® HELEX® Septal Occluder Feasibility Study Wire Frame Fractures Through 12-Month Follow-up Number of Subjects with Wire Frame Facture

	Time Post-Procedure			
Subjects Receiving Device (N=51)	**Pre Month 6 Follow-up**	**Month 6 Follow-up**	**Month 12 Follow-up**	**Overall**
Subjects Evaluable for Safety	51	46	43	51
Fracture-wire frame	-	1 (2.2%)	3 (7.0%)	4 (7.8%)

Note: Month 12 follow-up window extended through Day 548.

Of note:

- No device embolizations, device-related thrombus, strokes, perforations, or erosions were reported during the study follow-up.
- One subject experienced arrhythmia at 11 months post procedure that was treated with elective, transcatheter ablation of the SVT; the Data and Safety Monitoring Board (DSMB) determined that the event had an unknown relationship to the device.
- One subject experienced seizure events on Days 88 and 151 that were treated medically; the DSMB determined that the event had an unknown relationship to the device.

- Wire frame fractures were observed in 4 subjects (7.8%) through the 12-month follow-up. For all 4 subjects, the investigator and DSMB determined that no intervention was required; thus wire frame fractures not requiring intervention were subsequently considered minor adverse events by the study DSMB, so that the events would continue to be reported and tracked. However, these 4 subjects did not experience decreased efficacy because of wire frame fractures, an observation that remained consistent for a majority of the wire frame fractures across the clinical studies.
- There were no repeat procedures to the device or target ASD in the study population.

Of subjects evaluated for 12-month ASD closure by independent echocardiography core laboratory review, 94.6% (35/37) had clinically successful defect closure. Clinically significant leaks were present in two subjects (5.4%) at the 12 month follow-up evaluation. No subsequent follow-up was available on these 2 subjects. Clinical success, a composite of safety (no major adverse events) and efficacy (clinical closure at 12 months), was achieved in 89.5% of subjects available for evaluation (34/38). A hospital stay of 1 day or less was reported for 98% (50/51) subjects.

The Feasibility Study confirmed the safety and device performance for progression to a pivotal study to establish the safety and efficacy of the device compared to the surgical standard.

4. Multicenter Pivotal Study

The **Multicenter Pivotal Study** was a non-randomized, prospective, controlled study comparing safety and efficacy outcomes of the GORE® HELEX® Septal Occluder with traditional (open) surgical repair of atrial septal defects; this study was intended to demonstrate non-inferiority of device closure compared to surgical closure. Between March, 2001, and April, 2003, 119 subjects at 14 US sites received the GORE® HELEX® Septal Occluder and were compared to 128 control arm subjects treated by open heart surgical closure. All subjects were followed for one year post procedure/surgery.

a) Device Treatment Arm

Median age of device subjects was 6 years and 87% were less than 21 years old. One or more major adverse events were reported in seven subjects (5.9%) in the device arm through the 12-month follow-up, as presented in **Table 10**. A total of 11 major adverse events were reported in the seven subjects. A summary of wire frame fractures is presented in **Table 11.**

Table 10. GORE® HELEX® Septal Occluder Pivotal Study – Device Arm Major Adverse Events Through 12-Month Follow-up Number of Subjects by Type of Adverse Event and Timing of Onset

	Time Post-Procedure			
Subjects Receiving Device (N=119)	**Days 0-1**	**Days 2-30**	**Day 31 - Month 12**	**Overall**
Subjects Evaluable for Safety	119	117	115	119
Subjects With One or More Major Adverse Events	5 (4.2%)	2 (1.7%)	1 (0.9%)	7 (5.9%)
Device size inappropriate	2 (1.7%)	-	-	2 (1.7%)
Embolization (post- procedure)	2 (1.7%)	-	-	2 (1.7%)
Migraine (new)	-	2 (1.7%)	-	2 (1.7%)
Allergic reaction	-	1 (0.9%)	1 (0.9%)	1 (0.8%)
Hemorrhage (treatment or intervention required)	1 (0.8%)	-	-	1 (0.8%)
Paresthesia	-	1 (0.9%)	-	1 (0.8%)

Notes: Month 12 follow-up window extended through Day 548; One subject experienced a major nickel allergy event at Days 30 and 129 and also a major migraine and paresthesia

Of note:

- Device embolizations were reported in 2 subjects (1.7%) within 24 hours of index procedure. Both devices were recovered via catheter and the defect closed using an alternative device.
- Wire frame fractures were reported in 6 subjects (5.0%) through the 12-month follow-up. For all 6 subjects, the investigator determined that no intervention was required. The DSMB adjudicated these as minor adverse events with no deleterious impact on the patient or the closure status.
- No device-related thrombus, strokes, arrhythmias requiring treatment, perforations, or erosions were reported during the study follow-up.
- In 2 subjects, the device size was determined to be inappropriate for either defect size or anatomy and the physician elected to surgically close the defect the day following the index procedure. The device was safely removed during the surgical procedure.
- One subject experienced an allergic reaction potentially related to the nickel in the device's wire frame. The subject also reported major migraine and paresthesia adverse events as symptoms of the reaction. As a result, the physician and family elected to remove the device and close the defect surgically. The device was safely removed during the surgical procedure. The subject subsequently had a similar reaction to the stainless steel sternal wires, necessitating their removal as well.

Table 11. GORE® HELEX® Septal Occluder Pivotal Study – Device Arm Wire Frame Fractures Through 12-Month Follow-up Number of Subjects with Wire Frame Facture by Timing of Onset

	Time Post-Procedure			
Subjects Receiving Device (N=119)	**Pre Month 6 Follow-up**	**Month 6 Follow-up**	**Month 12 Follow-up**	**Overall**
Subjects Evaluable for Safety	119	112	107	119
Fracture-wire frame	-	3 (2.7%)	3 (2.8%)	6 (5.0%)

Note: Month 12 follow-up window extended through Day 548.

Clinically successful closure, as determined by independent echocardiographic core laboratory review, was achieved in 98.1% (103/105) of subjects evaluated at 12 months post-procedure. No subsequent follow-up was available on the two subjects determined to have clinically significant residual shunts. The primary clinical success endpoint was achieved in 91.7% (100/109) of subjects evaluated. A hospital stay of 1 day or less was reported for 96% (114/119) of subjects.

b) Surgical Control Arm

- Median age of surgical control subjects was 4 years and 92% were less than 21 years old. One or more major adverse events were reported in 14 subjects (10.9%) in the surgical control arm through the 12-month follow-up, as presented in **Table 12**. A total of 15 major adverse events were reported in the 14 subjects.

Table 12. GORE® HELEX® Septal Occluder Pivotal Study – Surgical Control Arm Major Adverse Events Through 12-Month Follow-up Number of Subjects by Type of Adverse Event and Timing of Onset

	Time Post-Procedure			
Surgical Arm (N=128)	**Days 0-1**	**Days 2-30**	**Day 31 - Month 12**	**Overall**
Subjects Evaluable for Safety	128	108	106	128
Subjects With One or More Major Adverse Events	2 (1.6%)	8 (7.4%)	4 (3.8%)	14 (10.9%)
Post-Pericardiotomy Syndrome	-	6 (5.6%)	2 (1.9%)	8 (6.3%)
Anemia	-	1 (0.9%)	-	1 (0.8%)
Bleeding (treatment required)	1 (0.8%)	-	-	1 (0.8%)
Hemorrhage (treatment or intervention required)	1 (0.8%)	-	-	1 (0.8%)
Hernia	-	-	1 (0.9%)	1 (0.8%)
Pulmonary Edema	-	1 (0.9%)	-	1 (0.8%)
Scarring or scar related	-	-	1 (0.9%)	1 (0.8%)
Stridor	-	1 (0.9%)	-	1 (0.8%)

Notes: Month 12 follow-up window extended through Day 548; One subject experienced major Pulmonary Edema and Anemia (Day 4)

Of note:

- Major complications from post-pericardiotomy syndrome were reported in 8 subjects (6.3%). Symptoms of post-pericardiotomy syndrome included pericardial or pleuriric pain, pleural effusions, pneumonitis, and abnormal ECG findings and were considered major when reintervention was required. Pericardiocentesis was reported as treatment in 5 subjects (3.9%). One subject (0.8%) required repeat pericardiostomy.
- One death resulting from complications of post-pericardiotomy syndrome was reported (pericardial effusions leading to tamponade).

Clinically successful closure, as determined by independent echocardiographic core laboratory review, was achieved in 100% (82/82) of subjects evaluated at 12 months post-procedure. Clinical success was achieved in 83.7% (72/86) of subjects evaluated. Median hospital stay was 3 days.

c) Summary

The comparative safety profile of the GORE® HELEX® Septal Occluder device is highlighted by the Kaplan-Meier analysis presented in **Figure 5** which provides an estimate of freedom from a major adverse event for both the device and surgical arms of the Multicenter Pivotal Study. The figure shows that, for both arms, major adverse events occur early post treatment and become rare after 3 months. At 12 months post procedure, 94.1% (95% CI: 89.9% to 98.3%) of patients were estimated to be free of a major adverse event in the device arm, while 87.6% (95% CI: 81.3% to 93.6%) were estimated to be free from a major adverse event in the surgical arm.

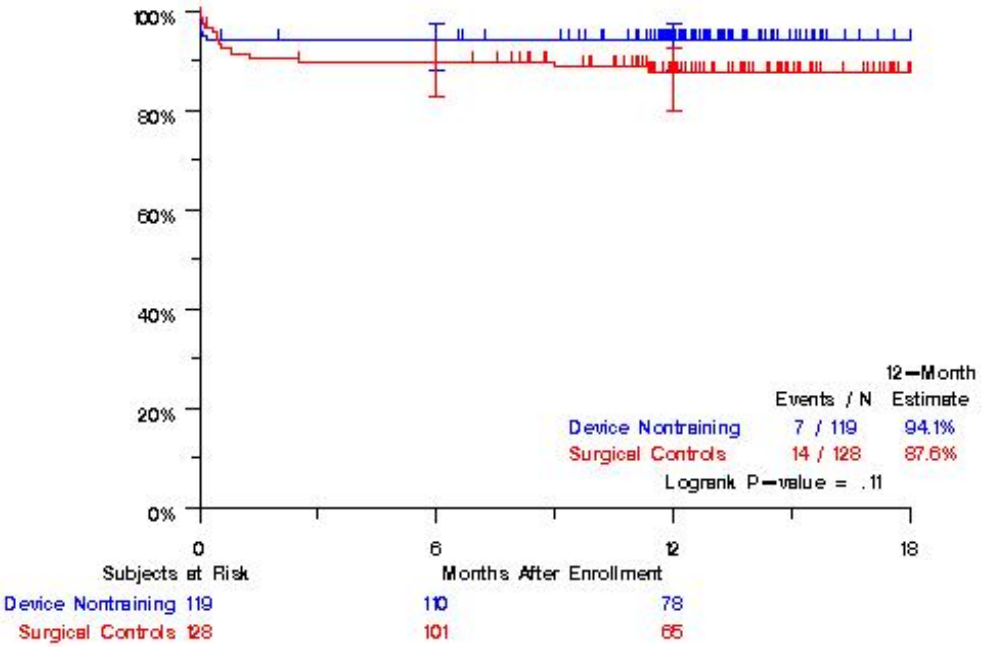

Figure 5. Freedom from a Major Adverse Event in Pivotal Study

The Multicenter Pivotal Study demonstrated the safety and efficacy of transcatheter treatment of *ostium secundum* ASD with the GORE® HELEX® Septal Occluder. Embolizations and wire frame fractures of the device were observed in the Pivotal Study device arm, however neither impacted subsequent treatment. No device-related thrombus, perforations, or erosions were reported.

The results of the Multicenter Pivotal Study also demonstrated that transcatheter treatment of *ostium secundum* ASD with the GORE® HELEX® Septal Occluder is a viable alternative to surgery through comparable clinical success and adverse event

outcomes. Patients successfully treated with the device avoided the trauma and scarring associated with an open procedure, and experienced shorter hospital stays.

5. Continued Access Study

The purpose of the **Continued Access Study** was to allow physicians to implant the GORE® HELEX® Septal Occluder during completion of the Multicenter Pivotal Study and approval process; and to collect safety and efficacy information on the final occluder device design iteration (GORE® HELEX® Septal Occluder 1.1 see **Table 6**). One hundred thirty-seven (137) subjects at 13 sites received the device in this study between May, 2003, and August, 2006. Median age was 5 years and 93% of subjects were less than 21 years old. All subjects were followed for 12 months post procedure. Pursuant to PMA approval conditions, the length of follow-up was expanded to five years post procedure. The post 12-month follow-up is presented in the Post Approval Study review.

One or more major adverse events were reported in 3 subjects (2.2%) through the 12-month follow-up, as presented in **Table 13**. A total of 3 major adverse events were reported in the 3 subjects. A summary of wire fractures is presented in **Table 14.**

Table 13. GORE® HELEX® Septal Occluder Continued Access Study Major Adverse Events Through 12-Month Follow-up Number of Subjects by Type of Adverse Event and Timing of Onset

	Time Post-Procedure			
Subjects Receiving Device (N=137)	**Days 0-1**	**Days 2-30**	**Day 31 - Month 12**	**Overall**
Subjects Evaluable for Safety	137	136	133	137
Subjects With One or More Major Adverse Events	2 (1.5%)	0 (0.0%)	1 (0.8%)	3 (2.2%)
Embolization (post- procedure)	2 (1.5%)	-	-	2 (1.5%)
Device removal due to fracture	-	-	1 (0.8%)	1 (0.7%)

Note: Month 12 follow-up window extended through Day 548.

Table 14. GORE® HELEX® Septal Occluder Continued Access Study Wire Frame Fractures Through 12-Month Follow-up Number of Subjects with Wire Frame Facture by Timing of Onset

	Time Post-Procedure			
Subjects Receiving Device (N=137)	**Pre Month 6 Follow-up**	**Month 6 Follow-up**	**Month 12 Follow-up**	**Overall**
Subjects Evaluable for Safety	137	128	125	137
Fracture-wire frame	3 (2.2%)	4 (3.1%)	3 (2.4%)	10 (7.3%)
Device removal due to fracture	1 (0.7%)	-	-	1 (0.7%)

Note: Month 12 follow-up window extended through Day 548.

Of note:

- Device embolizations were reported in 2 subjects (1.5%) within 24 hours of index procedure. Both devices were recovered via catheter and the defect closed using an alternative device.

- Wire frame fractures were reported in 10 subjects (7.3%) through the 12-month follow-up. Fracture led to device removal in 1 subject (0.7%) due to improper septal apposition. The device was successfully removed by catheter and an alternative device placed.
- No device-related thrombus, stroke, arrhythmias, perforations, or erosions were reported during the study follow-up.

Clinically successful closure, as determined by independent echocardiographic core laboratory review, was achieved in 99.1% (116/117) of subjects at 12 months post-procedure. No subsequent follow-up is currently available on the 1 subject determined to have a clinically significant residual shunt at 12 months. The primary clinical success endpoint was achieved in 96.7% (116/120) of subjects evaluated.

Results from the Continued Access Study supported the conclusion that the GORE® HELEX® Septal Occluder provides a safe and effective treatment option for patients with *ostium secundum* ASD and confirmed the safety and efficacy of the final device design.

6. Post Approval Study

The objective of the **Post Approval Study**, which currently remains in progress, is to evaluate the long-term safety and efficacy of the GORE® HELEX® Septal Occluder. This study included 87 subjects from the Continued Access Study; and an additional 128 device subjects enrolled between June, 2007, and October, 2008 from a total of 21 sites. Additionally, the first 50 subjects receiving the device in the Continued Access Study were followed to 5 years post procedure per FDA's conditions of approval. All 265 subjects are presented as part of the Post Approval Study cohort. The intent of this ongoing study is to follow subjects to five years post procedure. Data included for panel review are current as of March 2, 2012 and include events reviewed through January 12, 2012. The FDA reviews annual progress of the Post Approval Study and has determined Gore has maintained adequate progress towards completion of the study.

Median age of device subjects was 6 years and 87% were less than 21 years old. One or more major adverse event has been reported in 13 subjects (4.9%) in the long-term cohort to date, as presented in **Table 15**. A total of 16 major adverse events were reported in the 13 subjects. A summary of wire frame fractures is presented in **Table 16**.

Table 15. GORE® HELEX® Septal Occluder Post Approval Study Major Adverse Events Through Last Available Follow-up Number of Subjects by Type of Adverse Event and Timing of Onset

	Time Post-Procedure				
Subjects Receiving Device (N=265)	**Days 0-1**	**Days 2-30**	**Day 31 to Month 12**	**Months 24-60**	**Overall**
Subjects Evaluable for Safety	265	264	259	221	265
Subjects With One or More Major Adverse Events	5 (1.9%)	2 (0.8%)	5 (1.9%)	2 (0.9%)	13 (4.9%)
Device removal due to fracture	-	-	4 (1.5%)	1 (0.5%)	5 (1.9%)
Embolization (post- procedure)	4 (1.5%)	-	-	-	4 (1.5%)
Arrhythmia	-	1 (0.4%)	1 (0.4%)	1 (0.5%)	2 (0.8%)
Device Malposition	1 (0.4%)	-	-	-	1 (0.4%)
Headache	-	1 (0.4%)	-	-	1 (0.4%)
Valvular Damage	-	-	1 (0.4%)	-	1 (0.4%)
Other – Neurologic complication	-	1 (0.4%)	-	-	1 (0.4%)

Note: Month 12 follow-up window extended through Day 548, Month 60 follow-up extended through Day 2006.

Table 16. GORE® HELEX® Septal Occluder Post Approval Study Wire Frame Fractures Through 12-Month Follow-up Number of Subjects with Wire Frame Facture by Timing of Onset

	Time Post-Procedure				
Subjects Receiving Device (N=265)	**Pre Month 6 Follow-up**	**Month 6 Follow-up**	**Month 12 Follow-up**	**Months 24-60 Follow-up**	**Overall**
Subjects Evaluable for Safety	265	248	243	221	265
Fracture-wire frame	6 (2.3%)	9 (3.6%)	8 (3.3%)	3 (1.4%)	26 (9.8%)
Device removal due to fracture	3 (1.1%)	-	1 (0.4%)	1 (0.5%)	5 (1.9%)

Note: Month 12 follow-up window extended through Day 548, Month 60 follow-up extended through Day 2006.

One wire frame fracture, explanted at three years post procedure, was identified at the 6-month evaluation. The clinician continued to follow the subject and elected to remove the device (surgically) at 3 years because of a lack of improvement in septal apposition. The device removal due to fracture at 12 months was not identified until 9 months post procedure. The subject missed previous follow-up evaluations.

Of note:

- Device embolizations have been reported in 5 subjects (1.9%) within 24 hours of index procedure (2 reported previously in Continued Access summary). Four of 5 devices were recovered via catheter and the defect closed using an alternative device. In one subject the physician elected surgical closure and the device was removed during surgery.
- Wire frame fractures have been reported in 26 subjects (9.8%) through the 60-month follow-up (10 previously reported in Continued Access summary). Fractures led to removal of the device in 5 subjects due to improper septal apposition, device instability, and perforation of the mitral valve (described in next bullet). Four of 5 devices were removed during surgical repair of the defect.

- A wire frame fracture perforating the annular margin of the mitral valve was found at the 1-month follow-up in one subject. The device was removed and the defect and valve leaflet repaired surgically.
- Arrhythmia requiring treatment was reported in 2 subjects (0.8%; one subject at multiple time periods). Arrhythmia events resolved with medical treatment.
- No device-related thrombus, stroke, or erosions have been reported during the study follow-up.

Clinically successful closure, as determined by independent echocardiographic core laboratory review, was achieved in 99.1% (218/220) of subjects at 12 months and in 100% (87/87) of subjects evaluated to date at 60 months post-procedure. For one subject with a clinically significant leak at 12 months, core lab review determined the defect to be clinically successfully closed at 36 months. No subsequent follow-up is currently available on the other subject. A hospital stay of 1 day or less was reported for 97.7% (259/265) subjects.

The results to date of this ongoing study continue to confirm the safety and efficacy of the GORE® HELEX® Septal Occluder for the transcatheter treatment of *ostium secundum* ASD. The results also confirm the known safety profile of the device.

7. Analysis of Combined Clinical Study Data

A detailed review for each of the primary safety events of interest (erosion, device embolization, wire frame fracture, thrombus, stroke, etc.) is conducted in **Section V.** In this section, data from the 4 US clinical studies are combined to provide an overall view of the device's safety profile based on the clinical studies. Rationale for combining the clinical study data include:

- Inclusion/Exclusion criteria were similar across studies
- Evaluation and treatment protocols were similar
- Adverse event and study endpoint definitions were consistent across protocols
- The same external individuals were utilized for both the DSMB and independent Echocardiography Core Lab

The purpose of this section is to review the adverse event and wire frame fracture outcomes in the combined clinical study population in subgroups of interest, namely timing of the events and events by subject age, size of the defect, and nominal size of the received device. These more detailed reviews will demonstrate the consistent and predictable safety outcomes of the GORE® HELEX® Septal Occluder.

a) Subject Follow-up

Of the 435 subjects who received the GORE® HELEX® Septal Occluder in the combined studies, 170 were followed per protocol to one year and 265 will be followed to five years. All one year follow-up is completed. Follow-up to five years has been completed

in approximately one-half of the Post Approval Study subjects (**Figure 6**). Through March 2, 2012, these data represent approximately 1000 patient-years of follow-up.

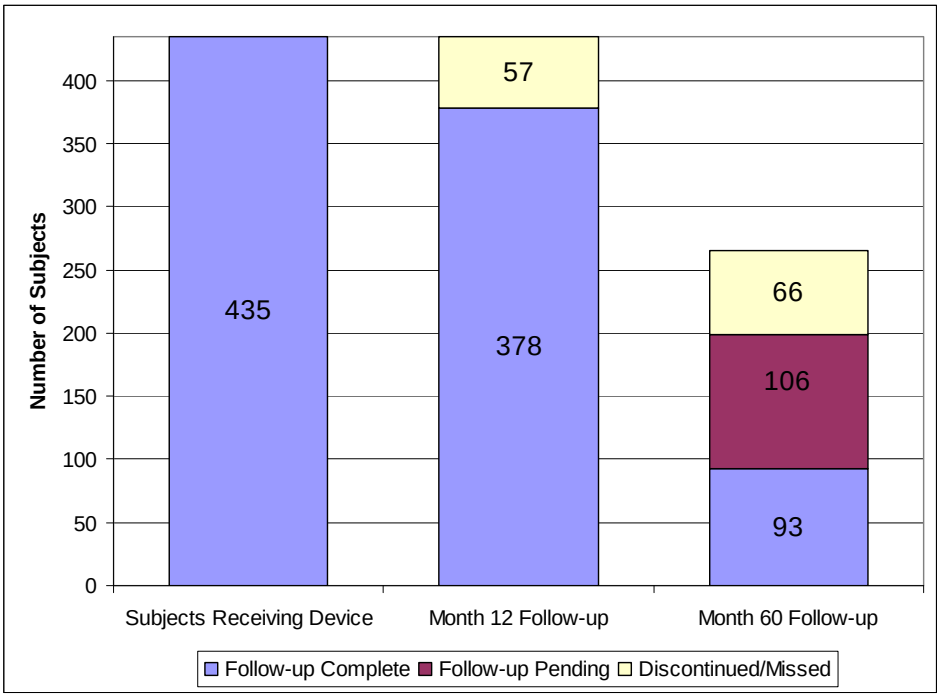

Figure 6. Follow-up Status of Subjects on Clinical Studies

b) Events by Timing of Event

Table 17 presents the major adverse events in the combined study population. A total of 28 major adverse events were reported in the 22 subjects. The major adverse events by timing of onset are presented in the table. Major adverse events primarily occurred early in follow-up. This conclusion is supported by the fact that 36% (10/28) of major adverse events occurred within the first 24 hours, 61% (17/28) cumulatively within the first 30 days, and 93% (26/28) cumulatively within the first year.

Table 17. Combined GORE® HELEX® Septal Occluder Clinical Studies Major Adverse Events Through Last Available Follow-up Number of Subjects by Type of Adverse Event and Timing of Onset

	Time Post-Procedure				
Subjects Receiving Device (N=435)	**Days 0-1**	**Days 2-30**	**Day 31 to Month 12)**	**Months 24-60**	**Overall**
Subjects Evaluable for Safety	435	432	424	221	435
Subjects With One or More Major Adverse Events	10 (2.3%)	4 (0.9%)	8 (1.9%)	2 (0.9%)	22 (5.1%)
Embolization (post- procedure)	6 (1.4%)	-	-	-	6 (1.4%)
Device removal due to fracture	-	-	4 (0.9%)	1 (0.5%)	5 (1.1%)
Arrhythmia	-	1 (0.2%)	2 (0.5%)	1 (0.5%)	3 (0.7%)
Device size inappropriate	2 (0.5%)	-	-	-	2 (0.5%)
Migraine (new)	-	2 (0.5%)	-	-	2 (0.5%)
Allergic reaction	-	1 (0.2%)	1 (0.2%)	-	1 (0.2%)
Device removal-other	1 (0.2%)	-	-	-	1 (0.2%)
Headache	-	1 (0.2%)	-	-	1 (0.2%)
Hemorrhage (treatment or intervention required)	1 (0.2%)	-	-	-	1 (0.2%)
Paresthesia	-	1 (0.2%)	-	-	1 (0.2%)
Seizure	-	-	1 (0.2%)	-	1 (0.2%)
Valvular Damage	-	-	1 (0.2%)	-	1 (0.2%)
Other - Neurologic complication	-	1 (0.2%)	-	-	1 (0.2%)

Note: Month 12 follow-up window extended through Day 548, Month 60 follow-up extended through Day 2006.

Table 18 presents the frequency of wire frame fractures and removals due to wire frame fracture in the combined study cohort by timing of fracture. The majority of wire frame fractures were discovered at the 6 and 12 month follow-up evaluations. Early (pre 6 months) fracture discoveries were more likely to result in device removals as fractures resulted in poor septal apposition and/or instability.

Table 18. Combined GORE® HELEX® Septal Occluder Clinical Studies Wire Frame Fractures Through Last Available Follow-up Number of Subjects with Wire Frame Facture by Timing

	Time Post-Procedure				
Subjects Receiving Device (N=435)	**Pre Month 6 Follow-up**	**Month 6 Follow-up**	**Month 12 Follow-up**	**Months 24-60 Follow-up**	**Overall**
Subjects Evaluable for Safety	435	406	393	221	435
Fracture-wire frame	6 (1.4%)	13 (3.2%)	15 (3.8%)	3 (1.4%)	36 (8.3%)
Device removal due to fracture	3 (0.7%)	-	1 (0.3%)	1 (0.5%)	5 (1.1%)

Note: Month 12 follow-up window extended through Day 548, Month 60 follow-up extended through Day 2006.

c) Events by Subject Age

Table 19 presents the major adverse events in the combined study cohort by age of the subject at procedure using the age classification categories from the GORE® HELEX® Septal Occluder PMA analysis. While 67% of the subjects were in the 2-11 years age

range, the data do not indicate a difference in risk of major adverse event by age category.

Table 19. Combined GORE® HELEX® Septal Occluder Clinical Studies Major Adverse Events Through Last Available Follow-up Number of Subjects by Type of Adverse Event and Age at Procedure

	Age at Procedure				
Subjects Receiving Device (N=435)	**Infant (< 2 yrs) (N=9)**	**Child (2-11 yrs) (N=293)**	**Adolescent (12-20 yrs) (N=77)**	**Adult (21+ yrs) (N=56)**	**Overall (N=435)**
Subjects With One or More Major Adverse Events	0 (0.0%)	14 (4.8%)	4 (5.2%)	4 (7.1%)	22 (5.1%)
Embolization (post- procedure)	-	3 (1.0%)	2 (2.6%)	1 (1.8%)	6 (1.4%)
Device removal due to fracture	-	3 (1.0%)	2 (2.6%)	-	5 (1.1%)
Arrhythmia	-	1 (0.3%)	-	2 (3.6%)	3 (0.7%)
Device size inappropriate	-	2 (0.7%)	-	-	2 (0.5%)
Migraine (new)	-	2 (0.7%)	-	-	2 (0.5%)
Allergic reaction	-	1 (0.3%)	-	-	1 (0.2%)
Device malposition	-	1 (0.3%)	-	-	1 (0.2%)
Headache	-	1 (0.3%)	-	-	1 (0.2%)
Hemorrhage (treatment or intervention required)	-	-	-	1 (1.8%)	1 (0.2%)
Paresthesia	-	1 (0.3%)	-	-	1 (0.2%)
Seizure	-	1 (0.3%)	-	-	1 (0.2%)
Valvular Damage	-	1 (0.3%)	-	-	1 (0.2%)
Other – Neurologic complication	-	1 (0.3%)	-	-	1 (0.2%)

Table 20 presents the frequency of wire frame fractures and removals due to wire frame fracture in the combined study cohort by age of the subject at procedure. The proportion of subjects reporting a wire frame fracture increases with increasing age categories. Given that older subjects generally received larger sized devices, this increase can be explained by the higher rate of wire frame fractures in larger device sizes (presented below).

Table 20. Combined GORE® HELEX® Septal Occluder Clinical Studies Wire Frame Fractures Through Last Available Follow-up Number of Subjects with Wire Frame Facture by Age at Procedure

	Age at Procedure				
Subjects Receiving Device (N=435)	**Infant (< 2 yrs) (N=9)**	**Child (2-11 yrs) (N=293)**	**Adolescent (12-20 yrs) (N=77)**	**Adult (21+ yrs) (N=56)**	**Overall (N=435)**
Fracture-wire frame	-	19 (6.5%)	9 (11.7%)	8 (14.3%)	36 (8.3%)
Device removal due to fracture	-	3 (1.0%)	2 (2.6%)	-	5 (1.1%)

d) Events by Device to Defect Ratio

Table 21 presents the major adverse events in the combined study cohort by the nominal device size to defect size ratio. Of note, no device embolizations have been reported in subjects where the device-to-defect ratio was 2:1 or greater.

Table 21. Combined GORE® HELEX® Septal Occluder Clinical Studies Major Adverse Events Through Last Available Follow-up Number of Subjects by Type of Adverse Event and Device-to-Defect Ratio

	Device to Defect Ratio			
Subjects Receiving Device (N=435)	**< 1.6 (N=33)**	**1.6 - < 2.0 (N=164)**	**2.0 + (N=238)**	**Overall (N=435)**
Subjects With One or More Major Adverse Events	4 (12.1%)	6 (3.7%)	12 (5.0%)	22 (5.1%)
Embolization (post- procedure)	1 (3.0%)	5 (3.0%)	-	6 (1.4%)
Device removal due to fracture	-	-	5 (2.1%)	5 (1.1%)
Arrhythmia	1 (3.0%)	1 (0.6%)	1 (0.4%)	3 (0.7%)
Device size inappropriate	1 (3.0%)	-	1 (0.4%)	2 (0.5%)
Migraine (new)	-	-	2 (0.8%)	2 (0.5%)
Allergic reaction	-	-	1 (0.4%)	1 (0.2%)
Device malposition	-	-	1 (0.4%)	1 (0.2%)
Headache	-	-	1 (0.4%)	1 (0.2%)
Hemorrhage (treatment or intervention required)	-	-	1 (0.4%)	1 (0.2%)
Paresthesia	-	-	1 (0.4%)	1 (0.2%)
Seizure	1 (3.0%)	-	-	1 (0.2%)
Valvular Damage	-	-	1 (0.4%)	1 (0.2%)
Other – Neurologic complication	-	-	1 (0.4%)	1 (0.2%)

Table 22 presents the frequency of wire frame fractures and removals due to wire frame fracture in the combined study cohort by the device-to-defect size ratio.

Table 22. Combined GORE® HELEX® Septal Occluder Clinical Studies Wire Frame Fractures Through Last Available Follow-up Number of Subjects with Wire Frame Facture by Device-to-Defect Ratio

	Device to Defect Ratio			
Subjects Receiving Device (N=435)	**< 1.6 (N=33)**	**1.6 - < 2.0 (N=164)**	**2.0 + (N=238)**	**Overall (N=435)**
Fracture-wire frame	3 (9.1%)	11 (6.7%)	22 (9.2%)	36 (8.3%)
Device removal due to fracture	-	-	5 (2.1%)	5 (1.1%)

e) Events by Defect Size

Table 23 presents the major adverse events in the combined study cohort by the size of the target defect. Device embolizations occurred more frequently in larger defects; however, as presented previously, no device embolizations have been reported in subjects where the device-to-defect ratio was at least 2:1.

Table 23. Combined GORE® HELEX® Septal Occluder Clinical Studies Major Adverse Events Through Last Available Follow-up Number of Subjects by Type of Adverse Event and Defect Size

	Defect Size				
Subjects Receiving Device (N=435)	**< 10mm (N=82)**	**10 - <14mm (N=144)**	**14 - <18mm (N=147)**	**18mm(+) (N=62)**	**Overall (N=435)**
Subjects With One or More Major Adverse Events	3 (3.7%)	1 (0.7%)	15 (10.2%)	3 (4.8%)	22 (5.1%)
Embolization (post- procedure)	-	1 (0.7%)	4 (2.7%)	1 (1.6%)	6 (1.4%)
Device removal due to fracture	2 (2.4%)	-	3 (2.0%)	-	5 (1.1%)
Arrhythmia	-	-	2 (1.4%)	1 (1.6%)	3 (0.7%)
Device size inappropriate	-	-	1 (0.7%)	1 (1.6%)	2 (0.5%)
Migraine (new)	-	-	2 (1.4%)	-	2 (0.5%)
Allergic reaction	-	-	1 (0.7%)	-	1 (0.2%)
Device malposition	1 (1.2%)	-	-	-	1 (0.2%)
Headache	-	-	1 (0.7%)	-	1 (0.2%)
Hemorrhage (treatment or intervention required)	-	-	1 (0.7%)	-	1 (0.2%)
Paresthesia	-	-	1 (0.7%)	-	1 (0.2%)
Seizure	-	-	1 (0.7%)	-	1 (0.2%)
Valvular Damage	-	-	1 (0.7%)	-	1 (0.2%)
Other – Neurologic complication	-	-	1 (0.7%)	-	1 (0.2%)

Table 24 presents the frequency of wire frame fractures and removals due to wire frame fracture in the combined study cohort by the size of the target defect. The proportion of subjects reporting a wire frame fracture increases with increasing defect size. Given that subjects with larger defects received larger sized devices, this increase can be explained by the higher rate of wire frame fractures in larger device sizes (presented below).

Table 24. Combined GORE® HELEX® Septal Occluder Clinical Studies Wire Frame Fractures Through Last Available Follow-up Number of Subjects with Wire Frame Facture by Defect Size

	Defect Size				
Subjects Receiving Device (N=435)	**< 10mm (N=82)**	**10 - <14mm (N=144)**	**14 - <18mm (N=147)**	**18mm(+) (N=62)**	**Overall (N=435)**
Fracture-wire frame	3 (3.7%)	4 (2.8%)	19 (12.9%)	10 (16.1%)	36 (8.3%)
Device removal due to fracture	2 (2.4%)	-	3 (2.0%)	-	5 (1.1%)

f) Events by Device Size

Table 25 presents the major adverse events in the combined study cohort by the nominal size of the implanted device. The higher frequency of major adverse events in the larger device sizes is driven in part by the higher frequency of embolizations or removals due to fracture.

Table 25. Combined GORE® HELEX® Septal Occluder Clinical Studies Major Adverse Events Through Last Available Follow-up Number of Subjects by Type of Adverse Event and Device Size

	GORE® HELEX® Device Nominal Size					
Subjects Receiving Device (N=435)	**15 mm (N=18)**	**20 mm (N=78)**	**25 mm (N=150)**	**30 mm (N=124)**	**35 mm (N=65)**	**Overall (N=435)**
Subjects With One or More Major Adverse Events	0 (0.0%)	0 (0.0%)	7 (4.7%)	8 (6.5%)	7 (10.8%)	22 (5.1%)
Embolization (post- procedure)	-	-	3 (2.0%)	1 (0.8%)	2 (3.1%)	6 (1.4%)
Device removal due to fracture	-	-	1 (0.7%)	1 (0.8%)	3 (4.6%)	5 (1.1%)
Arrhythmia	-	-	1 (0.7%)	1 (0.8%)	1 (1.5%)	3 (0.7%)
Device size inappropriate	-	-	-	1 (0.8%)	1 (1.5%)	2 (0.5%)
Migraine (new)	-	-	-	2 (1.6%)	-	2 (0.5%)
Allergic reaction	-	-	-	1 (0.8%)	-	1 (0.2%)
Device malposition	-	-	1 (0.7%)	-	-	1 (0.2%)
Headache	-	-	-	1 (0.8%)	-	1 (0.2%)
Hemorrhage (treatment or intervention required)	-	-	-	1 (0.8%)	-	1 (0.2%)
Paresthesia	-	-	-	1 (0.8%)	-	1 (0.2%)
Seizure	-	-	1 (0.7%)	-	-	1 (0.2%)
Valvular Damage	-	-	-	-	1 (1.5%)	1 (0.2%)
Other – Neurologic complication	-	-	-	1 (0.8%)	-	1 (0.2%)

Table 26 presents the frequency of wire frame fractures and removals due to wire frame fracture in the combined study cohort by size of the implanted device. Wire frame fractures occur with greater frequency in the larger size devices. However it is important to note that while fractures are more common in the larger size devices, very few devices were removed due to fractures. In the majority of subjects (31/36) the physician determined that the fracture did not impact the device's safety or efficacy to the point that removal of the device was in the subject's best interest.

Table 26. Combined GORE® HELEX® Septal Occluder Clinical Studies Wire Frame Fractures Through Last Available Follow-up Number of Subjects with Wire Frame Facture by Device Size

	GORE® HELEX® Device Nominal Size					
Subjects Receiving Device (N=435)	**15 mm (N=18)**	**20 mm (N=78)**	**25 mm (N=150)**	**30 mm (N=124)**	**35 mm (N=65)**	**Overall (N=435)**
Fracture-wire frame	-	-	3 (2.0%)	15 (12.1%)	18 (27.7%)	36 (8.3%)
Device removal due to fracture	-	-	1 (0.7%)	1 (0.8%)	3 (4.6%)	5 (1.1%)

g) Subset Analysis Conclusions

These subset analyses provide insight into the safety profile of the device across the range of potential patients and provide more information on the risk/benefit considerations. Important observations include:

- The probability of wire frame fracture increases with device size, however the subsequent need to remove the device remains low. Most wire frame fractures

are incidental findings that do not impact the safety or efficacy of the device, or outcomes for the patient.

- No device embolizations were reported in subjects where the device-to-defect ratio was 2:1 or greater. This finding was used in development of the 2:1 sizing recommendation that is found in the current IFU.
- Major adverse events beyond the 12 month follow-up were reported in 0.9% of subjects (<1%).
- Independent of device size and device-to-defect ratio, the data presented do not indicate that age of the subject is a factor in risk of major adverse event.
- The findings presented here confirm prior analyses on the PMA submission cohort by Latson et al. (2006, i.e. predictors of outcomes) and Fagan et al. (2009, predictors of wire frame fracture). These articles are provided in **Attachment 1** and **Attachment 8**, respectively.

h) Treatment for Major Adverse Events

The type of treatment reported for each major adverse event is presented in **Table 27.** Surgical intervention was reported in 8 of the 22 subjects with major adverse events; resulting in a 1.8% surgical reintervention rate in the overall clinical study population.

Table 27. Combined GORE® HELEX® Septal Occluder Clinical Studies Reported Treatment for Major Adverse Events Number of Subjects by Adverse Event and Treatment Type

	Treatment for Event			
Subjects Receiving Device (N=435)	**Medical[1]**	**Transcatheter**	**Surgery**	**Overall (N=435)**
Number of Subjects Overall	6 (1.4%)	8 (1.8%)	8 (1.8%)	22 (5.1%)
Embolization (post- procedure)	-	5 (1.1%)	1 (0.2%)	6 (1.4%)
Device removal due to fracture	-	1 (0.2%)	4 (0.9%)	5 (1.1%)
Arrhythmia	2 (0.5%)	1 (0.2%)	-	3 (0.7%)
Device size inappropriate	-	-	2 (0.5%)	2 (0.5%)
Migraine (new)	2 (0.5%)	-	-	2 (0.5%)
Allergic reaction	-	-	1 (0.2%)	1 (0.2%)
Device malposition	-	1 (0.2%)	-	1 (0.2%)
Headache	1 (0.2%)	-	-	1 (0.2%)
Hemorrhage (treatment or intervention required)	1 (0.2%)	-	-	1 (0.2%)
Paresthesia	1 (0.2%)	-	-	1 (0.2%)
Seizure	1 (0.2%)	-	-	1 (0.2%)
Valvular Damage	-	-	1 (0.2%)	1 (0.2%)
Neurologic complication – Fatigue	1 (0.2%)	-	-	1 (0.2%)

[1] Includes transfusion for retroperitoneal bleed (hemorrhage) and cardioversion for arrhythmia

i) Major Adverse Events Resulting in Device Removals

Overall, major adverse events resulting in device removal were reported in 15 (3.4%) of the 435 device subjects. The reasons for device removal included device embolization (6), wire frame fracture resulting in device instability or inadequate septal apposition (5), device sizing concerns (2), device malposition (1), and a potential nickel allergy (1). Of

these reinterventions, 47% were accomplished via a second transcatheter procedure, while the remaining 53% involved a surgical procedure.

A Kaplan-Meier estimate of freedom from device removal in the combined clinical studies population is presented in **Figure 7.** The 3-year estimate of freedom from reintervention is 96.7% (95% CI: 95.0% to 98.4%). This highlights that the majority of device removals occur soon after the procedure (within a few days for device embolizations and sizing concerns, and a few months for removals due to fractures) and become infrequent later in follow-up (1 device removed after 12-month follow-up).

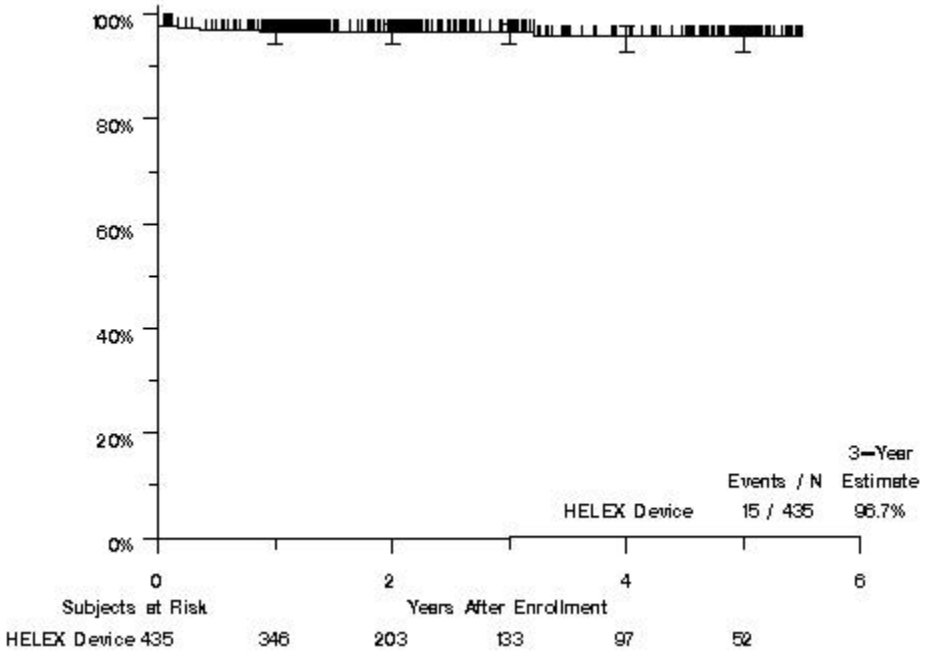

Figure 7. Freedom from Device Removal In The Combined Clinical Studies

j) Efficacy: ASD Closure

Combined data on ASD closure in subjects receiving the GORE® HELEX® Septal Occluder, as evaluated by the independent echocardiography core lab, are presented in **Table 28**. To date, no clinically significant leaks have been reported in subjects evaluated by the core lab at the 60 month evaluation in the ongoing Post Approval Study. Clinically significant leaks were found in 6 subjects (1.7%) at the 12-month evaluation. In 4 of the 6 subjects, study follow-up concluded at 12 months. For 1 subject, subsequent follow-up at 36 months found that the subject now had clinically successful defect closure. Additional follow-up on defect closure is pending for the remaining subject.

Table 28. Combined GORE® HELEX® Septal Occluder Clinical Studies Residual Defect Status: Echocardiography Core Lab Review

Subjects Receiving Device (N=435)	12 Months	36 Months	60 Months
Subjects with Core Lab Review	356	127	87
Clinically Successful Closure	350 (98.3%)	126 (99.2%)	87 (100%)
Clinically Significant Leak	6 (1.7%)	1 (0.8%)	0 (0.0%)

Note: Month 12 follow-up window extended through Day 548, Month 36 follow-up extended through Day 1276, Month 60 follow-up extended through Day 2006.

k) Risk/Benefit Assessment – Clinical Study Data

To place into perspective the risks and benefits of use of the GORE® HELEX® Septal Occluder in *ostium secundum* ASD closure, major adverse events and treatments for major adverse events were combined with successful treatment outcomes**. Table 29** details the patient outcomes of all implants, i.e. whether or not a further intervention was required after treatment with the GORE® HELEX® Septal Occluder, in the combined clinical studies. From this analysis, 96.3% of patients did not need a future surgical or transcatheter procedure.

Table 29. Combined GORE® HELEX® Septal Occluder Clinical Studies Patient Outcomes After Receiving Device

Subjects Receiving Device (N=435)	N (%)
No Intervention, or Medical Only	419 (96.3%)
Catheter Intervention	8 (1.8%)
Surgical Intervention	8 (1.8%)

8. Conclusions of Clinical Studies

The GORE® HELEX® Septal Occluder clinical trial data support the positive risk/benefit profile associated with the device's use. Patients treated with the GORE® HELEX® Septal Occluder are able to avoid the trauma and scarring associated with open surgical repair, as well as the extended hospital stay that surgical repair requires. These patients experienced successful efficacy outcomes, i.e. the device effectively closed the defect.

With regard to identified risks, a small percentage of patients experienced major adverse events. Post-procedure device removal was required in 3.4% of patients, 40% of these were accomplished via a subsequent transcatheter procedure. The leading cause for device removal was device embolization, occurring in 1.4% of patients (all of which received an undersized device per Gore's current recommendations). Additionally, removals due to wire frame fractures occurred in 1.1% of patients due to septal apposition and/or device instability. Noteworthy, ***none of these events*** required an emergency conversion to surgery.

The outcomes in the combined clinical studies highlight the key safety considerations of the GORE® HELEX® Septal Occluder defined and confirmed through these studies:

- No device or procedure-related deaths were reported in the clinical studies.

- Device embolization occurred in 1.4% (6). Most (5/6) device embolizations were removed via a repeat transcatheter procedure. All device embolizations occurred in cases where the nominal device diameter was less than twice the balloon sized defect diameter. This information highlights the importance of adhering to the recommended sizing recommendations, i.e. a 2:1 nominal device diameter to defect diameter ratio.
- Wire frame fractures occurred in 8.3% (26) overall and were higher in larger devices. Wire frame fractures leading to device removal are not common; occurring in 1.1% (5) of subjects.
- Arrhythmia requiring treatment potentially related to the device and/or procedure is rare (<1%).
- No reports of device-related thrombus or tissue erosions were observed acutely or in follow-up.
- No major adverse events were observed that required an emergency conversion to surgery.
- Current sizing recommendations included in the device's *Instructions for Use* are sufficient for minimizing the risks identified in the clinical study data.

The clinical data demonstrate the safety and effectiveness of the GORE® HELEX® Septal Occluder. The clinical studies served to outline the scope of potential major adverse events and no new or unanticipated adverse events were revealed over time. Incidence rates of adverse events did not increase over time. These data confirm that the benefits of device use, according to its approved labeling, continue to outweigh any observed risks of such use. These clinical data support the continued clinical use of the GORE® HELEX® Septal Occluder as a safe and effective treatment option for patients needing repair of *ostium secundum* ASD.

C. Post FDA Approval Worldwide ASD Closure Experience

1. Introduction

Within this section, Medical Device Reports (MDRs) and Gore's product surveillance data are assessed to elucidate the type and frequency of reported adverse events, as well as the impact of these events on the risk/benefit profile associated with the use of the GORE® HELEX® Septal Occluder.

Gore's Field Sales Associates and Clinical Specialists, whether in the US or outside the US, are present at approximately 80 to 90 percent of GORE® HELEX® Septal Occluder cases. These associates are specifically trained to report all observed events that bear on product quality or user satisfaction. These reports are then investigated for reporting to FDA as required. While generally MDRs are thought to reflect an under-reporting of adverse events, Gore believes it captures as many as reasonably possible.

It is noteworthy that no late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions. Additionally, the majority of major adverse events reported did not require surgical

intervention for event resolution. Medical Device Reports and physician reported patient outcomes continue to affirm the positive risk/benefit ratio associated with the use of the GORE® HELEX® Septal Occluder.

2. Medical Device Reports (MDRs)

In compliance with 21 CFR Section 803 (Medical Device Reporting), Gore reports adverse events associated with the use of the GORE® HELEX® Septal Occluder to FDA. Events were reported ***regardless of the application in which the product was used or where in the world the event occurred***. MDR reporting began following commercial approval of the device on August 11, 2006.

Examples of reportable events from Gore's quality system include the following:

- Device-related deaths
- Reintervention that appears to be related to the device
- Post-procedural device embolization
- Access Site Issues including unplanned surgical repair or reintervention related to access site complications that occur as a result of the removal of a device
- Wire Frame Fracture in the presence of conditions likely to result in reintervention
- Significant residual shunts likely to require reintervention
- Surgical conversion occurring during the primary procedure, except in cases where the physician determines during the interventional cardiology procedure that the subject's anatomy is more appropriately closed by a surgical procedure.
- Surgical reintervention

3. Assessment of MDR Reportable Events

A review of the MAUDE database was performed. A query of this database was conducted to determine the number of unique events involving the GORE® HELEX® Septal Occluder reported between August 11, 2006 (i.e., the date of PMA approval) and December 31, 2011. Each event was evaluated according to the frequency, the event type, and the resulting treatment required.

Figure 8 depicts the classification of MDR events for subsequent analysis. Two sets of data were identified: 1) the number of events utilized in ASD applications, i.e. **89** unique events; and 2) all reportable events, regardless of the application in which the product was used, i.e. **159** unique events including the 89 ASD events. Full details regarding this methodology are provided in **Attachment 9: Methodology for MDR Review.**

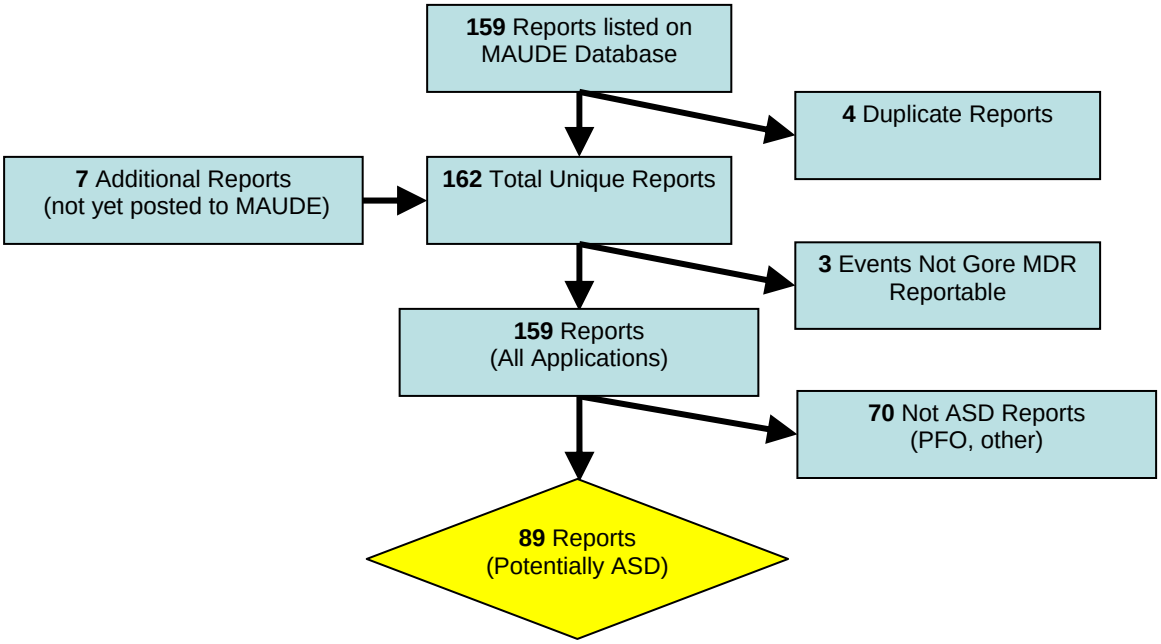

Figure 8. MAUDE Database Reports Involving the GORE® HELEX® Septal Occluder – August 11, 2006 – December 31, 2011

4. Estimates of Implanted Devices (Denominator)

Gore tracks the number of devices sold to individual hospitals. The number of devices implanted, however, is not absolutely known. Thus, an estimate is required. For this assessment, the number of devices sold for clinical and commercial use through December 31, 2011, both within and outside the US was considered (**Table 30**).

Table 30. Units Sold of GORE® HELEX® Septal Occluder

	Pre FDA Approval	Post FDA Approval	
	Summer 1999 - August 2006	**September 2006 - December 2011**	**Total**
All Regions	**3,312**	**16,875**	**20,187**
Within United States	509	13,541	14,050
Outside United States	2,803	3,334	6,137

By evaluating purchasing and stocking data, Gore estimates that 63% to 91% of devices sold are implanted in patients. Using these estimates, a reasonable range of actual event rates can be calculated.

Additionally, as the assessments provided in this document discuss the total number of events for ASD cases, devices implanted in the ASD application were estimated. Specifically, 56% of the GORE® HELEX® Septal Occluder MDR reports occurred during

use of the device in the ASD closure application. For the analysis presented in this document, 56% of implants were assumed to be in the ASD application.

Table 31 reflects the estimates of devices implanted, by application. For purposes of this analysis, all event rates are given as a range, based on both the higher and lower estimates of a likely implant denominator. This method attempts to place boundaries on the uncertainty of the actual adverse event rate.

Table 31. Estimated Implants of GORE® HELEX® Septal Occluders

	Pre FDA Approval		Post FDA Approval		Total	
	Lower Estimate	Upper Estimate	Lower Estimate	Upper Estimate	Lower Estimate	Upper Estimate
All Applications	**2,109**	**2,892**	**10,576**	**15,292**	**12,685**	**18,184**
ASD Only	1,181	1,619	5,920	8,560	7,101	10,179
Other	928	1,273	4,656	6,732	5,584	8,005

5. Time Course and Frequency of Worldwide Reportable Events, ASD Application

All **89** MDR events in the ASD application, occurring between August 11, 2006 (i.e., date of FDA Approval) and December 31, 2011 worldwide were analyzed to identify the time course (by event date) of reportable issues associated with the clinical use of the GORE® HELEX® Septal Occluder. Annual event frequency ranges were calculated per annual Post Approval ASD device implant estimates, using the same approach as described for total implant estimates.

Figure 9 illustrates the chronology and frequency of all MDR reportable events in the ASD application. The number of events per annum, and the event rate per estimated device implanted (with estimated range), are shown from the first incidence of a reportable event following PMA approval through December 31, 2011.

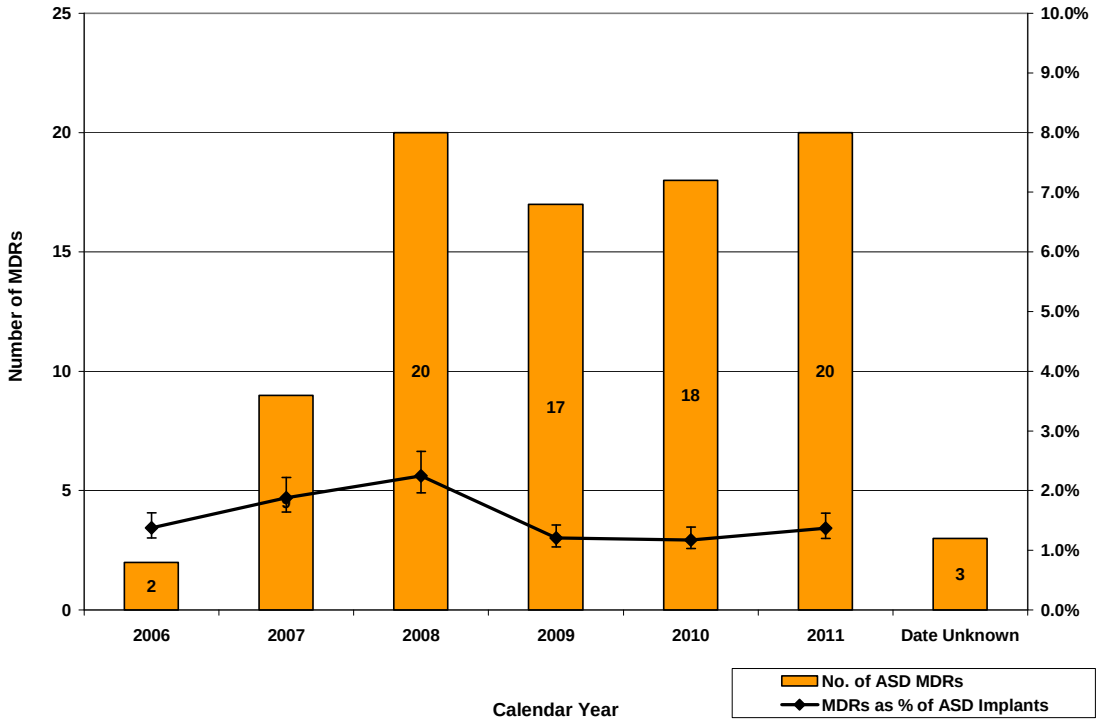

Figure 9. GORE® HELEX® Septal Occluder MDRs (ASD Application) by Calendar Year as % of Estimated Implants (October 2006-December 2011).
Error bars are estimated higher and lower rates based on lower and higher estimates of implants.

Noteworthy from this assessment is that the frequency of reportable events was low, and has not changed substantially since commercial approval of the device in August, 2006. **The average occurrence rate of MDR events worldwide was 1.3% (lower estimate = 1.1%, higher estimate = 1.5%)**. The low rate of adverse events seen throughout the commercial use of the device reaffirms the safety and efficacy findings of the US clinical studies.

6. Nature of Worldwide MDR Events, ASD Application

Each of the **89** MDR events associated with the use of the GORE® HELEX® Septal Occluder was reviewed to determine the nature of the adverse event. Reported adverse events were categorized according to the primary issue. Major categories included:

- Erosion, i.e. a device-anatomy interaction that causes a breakdown of the atrial wall resulting in hemodynamic compromise
- Perforation/Effusion (No erosion)
- Post-Procedural Device Embolization
- Malposition
- Residual/Recurrent Shunt

- Valve Dysfunction
- Fracture
- Peri-procedural Neurologic Events
- Device Thrombus
- Infection/Endocarditis/Sepsis
- Air Embolism
- Arrhythmia
- Allergy
- Others – including tissue entrapment, blood transfusion, removals for unknown reason, peripheral vessel damage/surgery

A summary of the review of this information, and the estimated worldwide ASD frequency (since FDA approval) of each event is presented in tabular and graphical formats in **Table 32** and **Figure 10**. Noteworthy, some subjects may have experienced more than one adverse event. Thus, the sum of the events exceed the total number of patients experiencing an adverse event.

Table 32. Nature and Frequency of Worldwide ASD MDR Reportable Events

Event Type	Total Occurrences	Estimated Occurrence Rate	
		Lower Estimate (N = 8,560)	Higher Estimate (N = 5,920)
Patients Experiencing One or More MDR event	**89**	**1.04%**	**1.50%**
Post-Procedural Device Embolization	34	0.40%	0.57%
Leak / Poor Apposition	31	0.36%	0.52%
Frame Fracture on Device Requiring Removal	11	0.13%	0.19%
Arrhythmia requiring ongoing treatment	10	0.12%	0.17%
Peripheral vessel damage / surgery	3	0.04%	0.05%
Thrombus	3	0.04%	0.05%
Effusions/tamponade, procedural	3	0.04%	0.05%
Effusion, post-procedural	2	0.02%	0.03%
Valvular Damage	2	0.02%	0.03%
Entrapment	2	0.02%	0.03%
Allergic Reaction	1	0.01%	0.02%
Death	1	0.01%	0.02%
Blood Transfusion	1	0.01%	0.02%
Surgical Removal (unknown reason)	1	0.01%	0.02%
Erosions	0	-	-

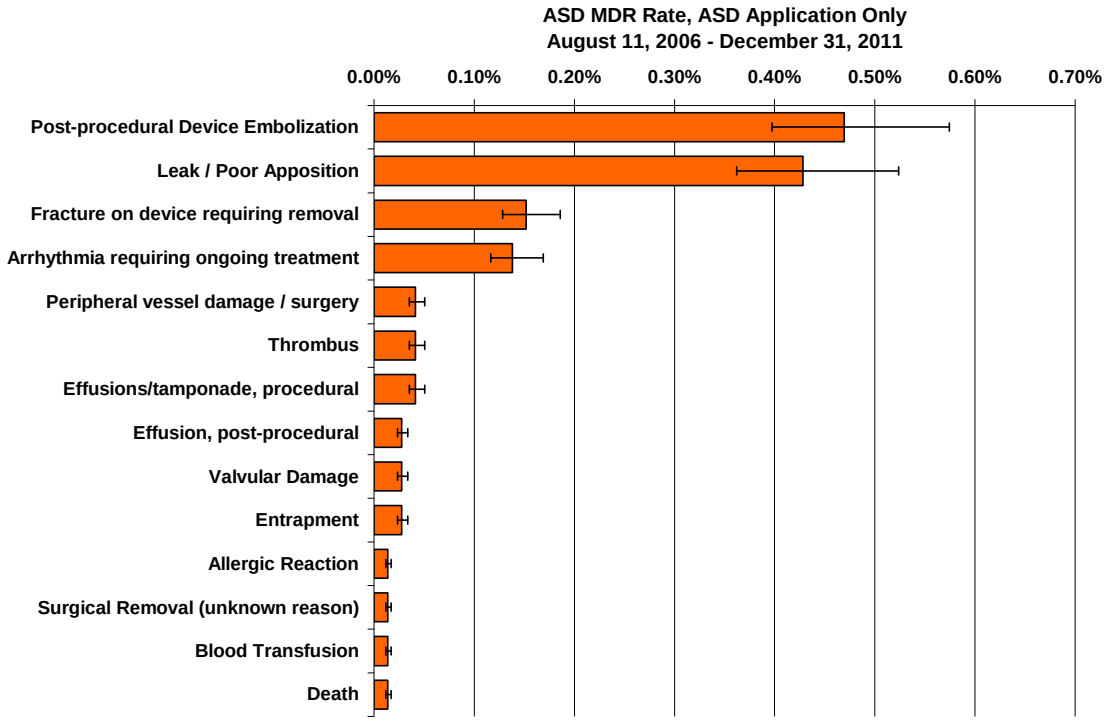

Figure 10. Major Adverse Event Rates from Worldwide MDRs, ASD Application.
Error bars are estimated higher and lower rates based on lower and higher estimates of implants.

In the ASD application, the leading issue of the MDR events involved with use of the GORE® HELEX® Septal Occluder was post-procedural device embolization, occurring at an estimated rate of 0.40% - 0.57%. The second most common adverse event involved residual leaks or poor device apposition.

One procedural death was noted in these data (see *MDR #2017233-2010-00103 / Gore Event #11462)*. This event involved a case in which an aortic valvuloplasty, AMPLATZER® occluder implant, and GORE® HELEX® Septal Occluder device implant were performed in the same procedure. During the course of the case, a pericardial effusion developed. After 4 hours of treatment for the effusion, the patient expired.

No late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions*, *or any events requiring late emergency device-related surgical intervention. A complete assessment of the major categories of safety issues is discussed in **Section V**.

7. Worldwide ASD MDRs by Resulting Treatment or Outcome

In addition to the nature of the MDR events discussed above, the data from the **89** ASD MDR reports in the ASD application were assessed to determine the resultant treatment

(intervention) or outcome for each patient. In this assessment 6 categories were utilized. They included:

- **No intervention** – These events were typically MDR Malfunction events that did not result in an injury to the patient.
- **Medical intervention** – Events that resolved with only medical therapy. An example would be an arrhythmia that resolved with steroid treatment or other medication. Additionally, cardioversion was included in this category.
- **Catheterization** – Events requiring a subsequent transcatheter procedure. These included recovery of an embolized device via a snare, or implantation of a second device to resolve a residual leak, or a catheter ablation to treat an arrhythmia.
- **Access site procedure** – Events including surgical cutdowns at the groin to permit entry or removal of a catheter or occluder.
- **Surgery** – Events requiring cardiac surgical treatment, such as removal of a device, subsequent surgical repair of a defect, pericardiocentesis, or implantation of a pacemaker.
- **Death**

The categories above are listed according to increasing severity. Each MDR event was assigned to only the most severe category that described the patient outcome due to the event. For example, an event involving transcatheter removal of an embolized device, but requiring a surgical cutdown at the femoral vein, would only be tallied within the Access site procedure category. Data from this analysis are presented in **Table 33** and **Figure 11**, below.

Table 33. Outcomes of Worldwide ASD Patients Experiencing an MDR Event

	ASD Application	MDR Outcome Rate
Patients Experiencing an MDR event with outcome	**89**	
No intervention	2	2.2%
Medical intervention	7	7.9%
Catheterization	41	46.1%
Access site procedure	2	2.2%
Surgery[1]	36	40.4%
Death	1	1.1%

[1] None of the post-procedural surgical interventions were performed on an emergency basis.

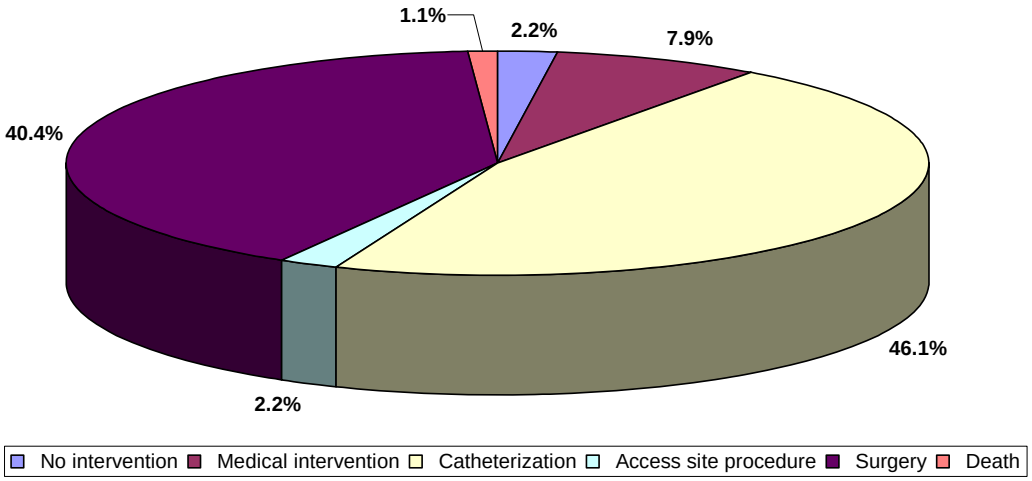

Figure 11. Outcomes of Patients Experiencing an MDR Event

In conclusion, ASD patients experiencing a reportable adverse event involving the GORE® HELEX® Septal Occluder were not susceptible to a high rate of severe complications. MDR data indicates a patient has an approximately 2% chance of experiencing an MDR-reportable adverse event with the GORE® HELEX® Septal Occluder. One death was identified from this cohort, involving a procedural complication during a complex case that involved multiple procedures and devices.

In the majority of cases experiencing an adverse event, the event was treated with a subsequent transcatheter procedure, medical intervention, groin cutdown, or no intervention at all. These patients received successful repair of their defect while avoiding the trauma, scarring and extended recovery associated with an open cardiovascular surgical procedure.

8. Risk/Benefit Assessment, Worldwide ASD MDR Data

To place into perspective the risks and benefits of use of the GORE® HELEX® Septal Occluder in *ostium secundum* ASD closure, data from the previous section was combined with successful treatment outcomes. **Table 34** and **Figure 12** report likely patient outcomes to be expected with the GORE® HELEX® Septal Occluder. Based on MDR data, approximately 98% of patients can expect one procedure without an MDR-reportable event. Approximately 2% of patients can expect a second procedure which is likely not to be surgical. These metrics compares favorably to the clinical success rates reported in the US clinical studies.

Table 34. Patient Outcome Frequency Associated with Estimated Implants

Patient Outcomes	ASD Implants		
	Lower Estimate (N=5,920)	Likely Estimate (N=7,240)	Higher Estimate (N=8,560)
No Adverse Event; No MDR; No Intervention or Medical Therapy	98.65%	98.90%	99.07%
Catheterization	0.69%	0.57%	0.48%
Access site procedure	0.03%	0.03%	0.02%
Surgery[1]	0.61%	0.50%	0.42%
Death	0.02%	0.01%	0.01%

[1] None of the post-procedural surgical interventions were performed on an emergency basis.

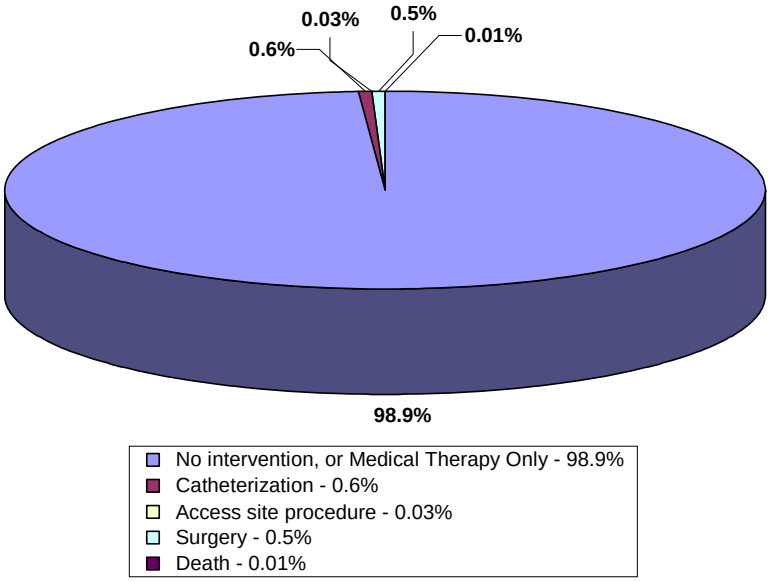

Figure 12. Post FDA Approval ASD Patient Outcomes, Estimate of Likely Further Intervention Required

9. Post FDA Approval Worldwide ASD Closure Experience Summary

Worldwide ASD data since FDA Approval in August, 2006 continue to support the conclusion that the benefits associated with use of the GORE® HELEX® Septal Occluder outweigh the potential risks. As with any medical procedure, serious adverse events may occur. In the case of this device, the most frequently encountered adverse events were post-procedural device embolization or reinterventions due to poor septal apposition or residual leaks. An assessment of each major adverse event type is provided in **Section V**.

No late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention. Adverse

events identified in the commercial use of the device were consistent with those identified or anticipated in the clinical studies, and with those listed in the product's labeling as potential adverse events.

D. Clinical Experience Summary

The information presented in the preceding sections summarize the safety profile of the use of the GORE® HELEX® Septal Occluder in the application of ASD closure, as observed in both the US clinical studies and the Post FDA Approval commercial experience. Both sources of data highlight the positive risk/benefit profile associated with the use of the device. The worldwide experience has ***not generated a single report of late adverse events that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention***.

Adverse event information from the clinical studies and commercial experience are compared below to demonstrate that the adverse event rates identified in the clinical studies were not markedly different from that observed in the commercial experience of the GORE® HELEX® Septal Occluder.

Table 35 provides a complete listing of major adverse events identified in Gore's clinical trial experience and Gore's worldwide commercial and clinical experience through December 31, 2011. Additionally, a third column highlights whether the adverse event is identified or otherwise described as a potential adverse event in the GORE® HELEX® Septal Occluder *Instructions for Use*.

Table 35. Comparison of Clinical Trial and Post FDA Approval ASD Experience Data

Subjects Retaining Device	Clinical Trial Data (N=435 patients)	Post FDA Approval ASD Commercial Experience (N=5,920 – 8,560 implants)	Complication Seen In Clinical Trial	Complication Noted in IFU
Estimated Major Adverse Event Rate	22 (5.1%)	89 (1.04% - 1.50%)	-	-
Apposition/Leak[1]	8 (1.8%)	31 (0.36% - 0.52%)	Yes	Yes
Embolization (post-procedure)	6 (1.4%)	34 (0.40% - 0.57%)	Yes	Yes
Fracture of device requiring removal	5 (1.1%)	11 (0.13% - 0.19%)	Yes	Yes
Arrhythmia requiring ongoing treatment	3 (0.7%)	10 (0.12% - 0.17%)	Yes	Yes
Valvular Damage	1 (0.2%)	2 (0.02% - 0.03%)	Yes	Yes
Access Site Bleed	1 (0.2%)	1 (0.01% - 0.02%)	Yes	Yes
Allergic reaction	1 (0.2%)	1 (0.01% - 0.02%)	Yes	Yes
Thrombus	0	3 (0.04% - 0.05%)	-	Yes
Peripheral vessel damage/surgery	0	3 (0.04% - 0.05%)	-	Yes
Effusion, or Tamponade (procedural)	0	3 (0.04% - 0.05%)	-	Yes
Effusion, post-procedural	0	2 (0.02% - 0.03%)	-	Yes
Entrapment	0	2 (0.02% - 0.03%)	-	Yes
Procedure-related Death[2]	0	1 (0.01% - 0.02%)	-	Yes
Surgical Removal (unknown cause)	0	1 (0.01% - 0.02%)	-	Yes
Erosions	0	0	-	Discussed as not occurring

[1] Apposition/Leak includes all reports of intervention for residual leaks and poor device apposition in the presence or absence of frame fractures.
[2] Procedural-related death involved a case with multiple interventions including the use of the GORE® HELEX® Septal Occluder.

As noted above, the adverse events noted throughout Gore's commercial experience with the GORE® HELEX® Septal Occluder do not indicate an adverse event rate in excess of what was observed in the US clinical studies. Events not encountered during the clinical trials, which were encountered in the commercial experience, are rare. These include thrombus formation, post-procedural effusions, entrapment, blood transfusions, and death. Each of these is appropriately documented as a potential adverse event within the product's *Instructions for Use*, as they are anticipated adverse events associated with septal defect closures and transcatheter procedures, generally.

Collectively, the clinical and commercial experiences with the GORE® HELEX® Septal Occluder highlight the following:

- Nominal device diameter to defect diameter ratio (i.e., device sizing) is important for clinical success.

  - The device may embolize if not correctly sized
- Complications surrounding the use of the GORE® HELEX® Septal Occluder are understood, and may be managed to provide clinical success. The majority of major adverse events encountered in conjunction with the use of the GORE® HELEX® Septal Occluder can be managed via a second catheterization procedure.
- The breadth of occluder-related major adverse event types that may occur have been adequately characterized in the clinical trials. Few new major occluder-related adverse events have appeared, and all are appropriately documented in the product's *Instructions for Use*
- ***No late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention.***

When utilized according to its *Instructions for Use*, the GORE® HELEX® Septal Occluder offers a safe and effective treatment option for patients with *ostium secundum* atrial septal defects, allowing patients to avoid the potential trauma and tissue scarring associated with a surgical procedure.

IV. NON-ASD CLINICAL EXPERIENCE

A. Analysis of Worldwide Experience, All Applications

Gore was asked by FDA to comment on the relevance of ASD safety date to the use of GORE® HELEX® Septal Occluder in other applications. To answer that question, Gore analyzed worldwide post approval experience in all applications. Similar to the analysis of ASD MDR events, the full history of worldwide GORE® HELEX® Septal Occluder experience was assessed from the date of first clinical use of the device in June, 1999, through December 31, 2011. This analysis of worldwide experience included 159 events: the **89** MDR events in the ASD application, the additional **70** MDR events from other applications. Serious adverse event types and event outcomes were assessed.

Each of the 159 adverse events associated with use of the GORE® HELEX® Septal Occluder was reviewed to determine the nature of the adverse events and categorized according to the primary issue, in the same way the ASD MDR events were assessed. While no statistical comparisons can be made from the worldwide post approval data, **Table 36** demonstrates the similarity of event types when the GORE® HELEX® Septal Occluder is used for ASD and non-ASD (mainly PFO) applications.

Table 36. Nature and Frequency of Worldwide Serious Adverse Events

Event Type	Post FDA Approval (ASD)	Post FDA Approval (non-ASD)
Patients Experiencing One or More Serious Adverse Event	**89**	**70**
Leak / Poor Apposition	31	30
Post-Procedural Device Embolization	34	17
Fracture on device requiring removal	11	4
Arrhythmia requiring ongoing treatment	10	7
Peripheral vessel damage / surgery	3	6
Effusions/tamponade, procedural	3	5
Thrombus	3	3
Retrieval cord left in patient	0	1
Valvular Damage	2	0
Entrapment	2	0
Allergic Reaction	1	1
Infection	0	1
Death	1	0
Procedural Stroke/TIA	0	1
Effusion, post-procedural	2	0
Air Embolism	0	1
Blood Transfusion	1	0
Surgical Removal (unknown reason)	1	0
Erosions	0	0

Throughout the worldwide, all-application history of the device, ***no late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention.*** A complete assessment of the major categories of safety issues is discussed in **Section V**.

B. Worldwide, All-Application Adverse Events by Resulting Treatment or Outcome

As was assessed for the ASD MDR reports, the 159 worldwide, all-application events were assessed to determine the resultant treatment (intervention) or outcome of each patient. The same six categories and approach were utilized. Data from this analysis is presented in **Table 37**.

Table 37. Outcomes of Worldwide, All-Applications Patients Experiencing a Serious Adverse Event

	Post FDA Approval (ASD)	Post FDA Approval (non-ASD)
Patients Experiencing One or More Serious Adverse Event	**89**	**70**
No intervention	2	6
Medical intervention	7	7
Catheterization	41	35
Access site procedure	2	6
Surgery[1]	36	16
Death	1	0

[1] None of the post-procedural surgical interventions were performed on an emergency basis.

Similar to the conclusion for ASD patients, the worldwide, all-application history of patients experiencing serious adverse events involving the GORE® HELEX® Septal Occluder illustrate a low rate of severe complications.

In the majority of cases reporting an adverse event, either ASD or non-ASD, the events were handled by a subsequent transcatheter procedure, medical intervention, groin cutdown, or no intervention at all. These patients received successful repair of their defect while avoiding the trauma, scarring and extended recovery associated with an open cardiovascular surgical procedure.

C. Risk/Benefit Assessment, Worldwide, All-Application Experience

Time course (by event date) of serious adverse events associated with the worldwide, all-application clinical use of the GORE® HELEX® Septal Occluder are presented in **Figure 13** on a per annum basis. Event frequency ranges were also calculated per the worldwide device implant estimates (lower estimate 12,685; higher estimate 18,184), in the same manner discussed above.

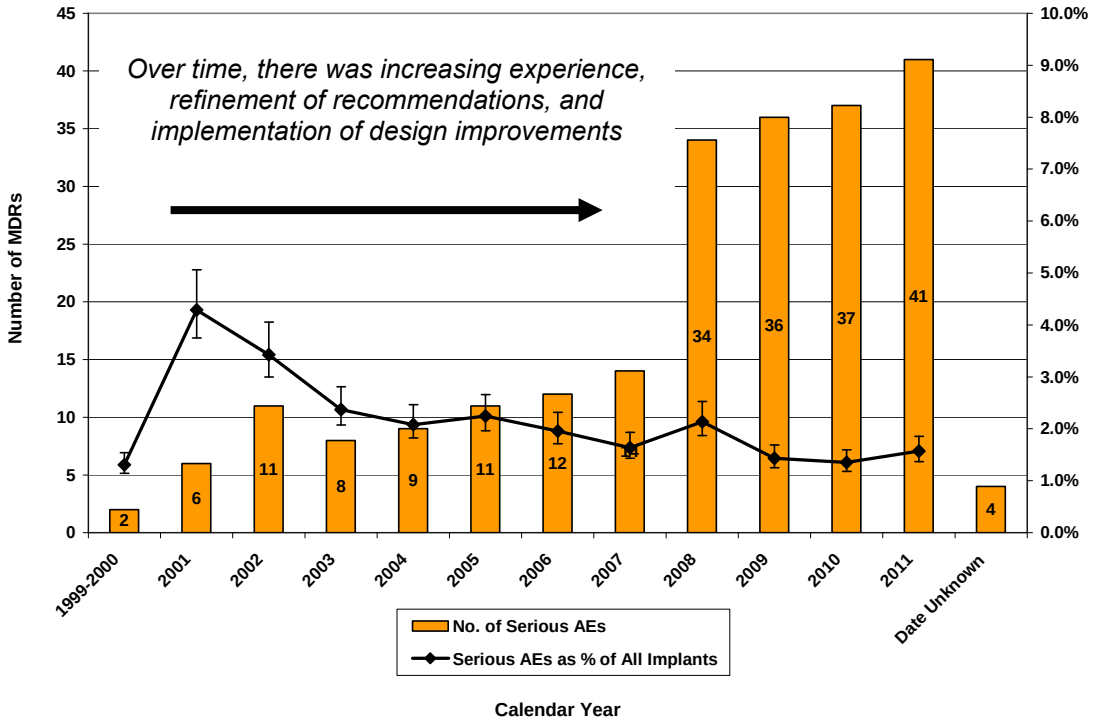

Figure 13. Worldwide GORE® HELEX® Septal Occluder Serious Adverse Events (All Applications) by Calendar Year as % of Estimated Implants (June 1999-December 2011).
Error bars are estimated higher and lower rates based on lower and higher estimates of implants.

Noteworthy from this assessment is that the frequency of serious adverse events tended to decrease with time. As has been discussed in this document, an understanding of appropriate applications, implementation of sizing recommendations, design improvements, and training programs all have helped to generate more positive patient outcomes with time. With this analysis, the worldwide **average occurrence rate of serious adverse events worldwide was 1.8% (lower estimate = 1.5%, higher estimate = 2.2%)**.

Table 38 and **Figure 14** depict the likely patient outcomes of all implants regardless of application, i.e. whether no further intervention was required after treatment with the GORE® HELEX® Septal Occluder. This metric compares favorably to the clinical success score reported in the US clinical studies for the ASD only application. In the case of the GORE® HELEX® Septal Occluder, ***98.8% of patients are likely to not require a future surgical or transcatheter procedure***.

Table 38. Patient Outcome Frequency Associated with Implants

Patient Outcomes	Worldwide, All-Applications		
	Lower Estimate (N=12,685)	Likely Estimate (N=15,435)	Upper Estimate (N=18,184)
No intervention, or Medical Therapy Only	98.54%	98.80%	98.98%
Catheterization	0.81%	0.67%	0.57%
Access site procedure	0.06%	0.05%	0.04%
Surgery[1]	0.57%	0.47%	0.40%
Death	0.02%	0.01%	0.01%

[1] None of the post-procedural surgical interventions were performed on an emergency basis.

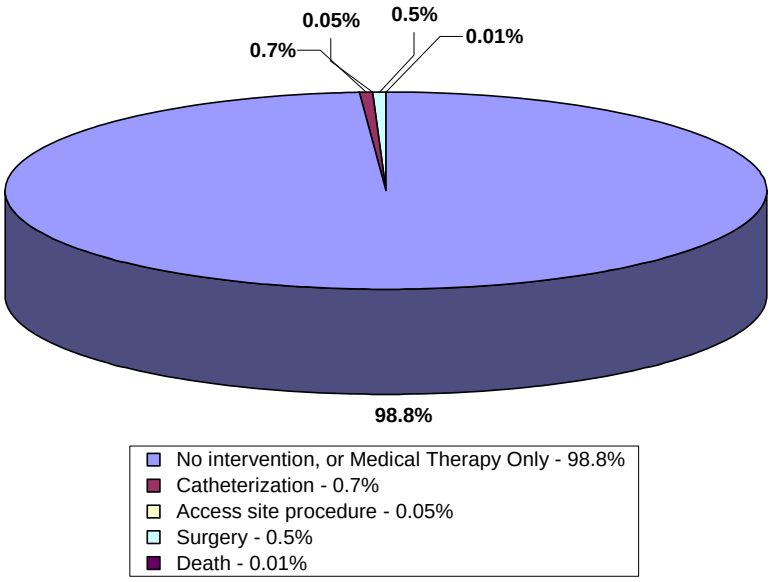

Figure 14. Worldwide, All-Application Patient Outcomes, Likely Estimate of Further Required Intervention

More information relevant to the questions of safety and effectiveness in the PFO application will be answered by the ongoing multi-national, multi-center Gore REDUCE Clinical Study. No data from the Gore REDUCE Clinical Study is included in this analysis, as Gore is blinded to the results of this trial. Worldwide data analyzed to date comparing ASD with all-application data indicates a similar safety profile, with little difference in the type or outcomes of treatment for adverse events. Therefore, Gore finds the safety and effectiveness data from ASD closure is relevant to the use of the device in non-ASD applications.

V. SAFETY

A. Introduction

FDA has advised sponsors and the panel to focus on adverse events of clinical significance to the patient, specifically: erosions, device embolizations, wire frame fractures, thrombus (stroke/TIA), and arrhythmia.

Within this section, an analysis of the potential safety issues related to the use of septal occluders is provided. Issues assessed include:

- Erosion
- Post-Procedural Device Embolization
- Frame Fracture
- Reintervention Due to Residual Shunt
- Arrhythmia
- Thrombus
- Other

Descriptions of each issue, their occurrence rate as determined through Gore's analysis of the clinical and commercial experience with the GORE® HELEX® Septal Occluder, and a discussion regarding risk mitigation for each adverse event type is provided.

B. Erosions

1. Description

Device erosion is a device-anatomy interaction that causes a breakdown of the atrial wall resulting in hemodynamic compromise. Pericardial effusions due to procedural issues, e.g. a guidewire perforation, etc., are not considered erosions.

2. Occurrence Rates

Gore has reviewed data from US Clinical Trials, MDRs and Serious Adverse Events from product surveillance of worldwide commercial use, and published literature for the GORE® HELEX® Septal Occluder regarding erosions. A total of **0 device erosions** of the aortic root or the free wall of the atria have been reported **in over 12 years of clinical experience with an estimated 12,685 to 18,184 devices implanted worldwide in all-use applications**. Gore continues to collect data regarding erosions from its Post Approval Study and worldwide product surveillance.

a) Analysis of FDA-Identified Events

Independent of Gore's analyses, FDA has searched the MAUDE database to identify possible reports of erosions. The search terms used were: perforation, tissue erosion, pericardial effusion (with or without drainage), pericardial tamponade, puncture, fissure,

aortic to atrial fistula, laceration, hemopericardium, penetration. FDA's search of the MAUDE database using these terms identified fifteen (15) MDRs for the GORE® HELEX® Septal Occluder that FDA has requested Gore evaluate as possible erosions. The algorithm for this evaluation was provided to Gore by FDA and is the decision tree being used to determine erosions with the St. Jude AMPLATZER® Septal Occluder (**Figure 15**).

The MDR events with the GORE® HELEX® Septal Occluder identified by FDA for evaluation as possible erosions include eight (8) in Potentially ASD and seven (7) in Not ASD (PFO, other) applications, as listed in **Table 39**. Gore has analyzed each of these events and determined that **none are erosions**, as shown in **Figure 16** and described in detail below. In presenting these events, the event descriptions are taken directly from the MAUDE database. Additional information about the event is provided by Gore, if needed, as well as a conclusion of the analysis for each event.

Table 39. GORE® HELEX® Septal Occluder MDRs Reviewed At FDA Request To Determine If They Are Erosions, Grouped By Application.

MDR #	Gore Event #	Application
2017233-2010-00103	11462	Potentially ASD
2017233-2009-00527	10808	
2017233-2010-00458	12785	
2017233-2010-00578	13289	
2017233-2008-00924	7586	
2017233-2010-00521	13074	
2017233-2011-00061	13598	
2017233-2008-00505	6885	
2017233-2008-00056	6198	Not ASD (PFO, other)
2017233-2008-00942	7591	
2017233-2009-00291	9576	
2017233-2010-00166	11811	
2017233-2010-00497	13073	
2017233-2010-00577	13363	
2017233-2009-00370	10050	

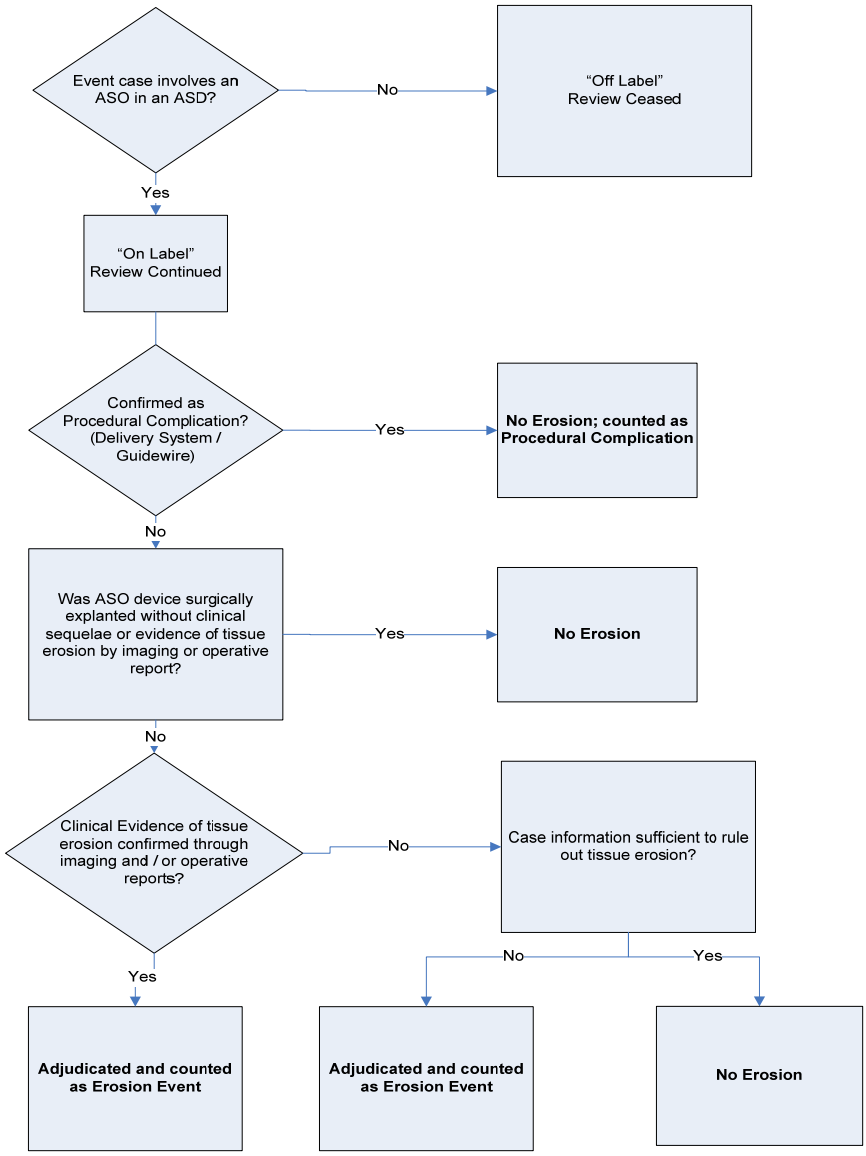

Figure 15. Decision tree for identifying erosions with the St. Jude AMPLATZER® Septal Occluder, as provided to Gore by FDA.

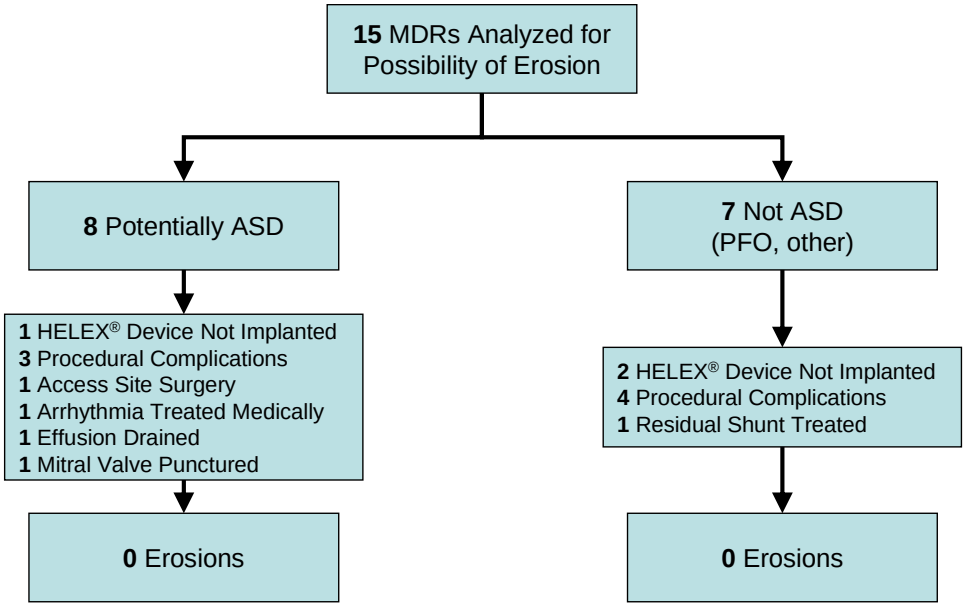

Figure 16. Summary of Analysis of 15 MDRs with the GORE® HELEX® Septal Occluder for Possibility of Erosion per FDA Request using St. Jude Erosion Algorithm.

Note to Reviewers: MAUDE narratives typically do not use trademarks correctly. Text is taken verbatim from the MAUDE database.

b) Analysis of MDRs Resulting from Erosion Query

Eight (8) of the MDRs occurred in Potentially ASD applications. These were each evaluated and determined to not be erosions per the St. Jude erosion algorithm:

MDR #2017233-2010-00103 / Gore Event #11462

"On (b) (6) 2010, the patient underwent aortic valvuloplasty to treat aortic valve stenosis. A 12mm amplatzer septal occluder was then selected to close an asd. Intracardiac echocardiography revealed that a significant shunt associated with a patent foramen ovale persisted. A 30mm helex device was advanced across the patent foramen ovale, deployed over the amplatzer device, and transesophageal echocardiography was performed which showed that the helex device was not adequately covering the secundum. During retrieval of the device, the retrieval cord broke. A coronary balloon was inflated inside the long sheath and the occluder and sheath were pulled down the ivc to the access site. Tee showed that a pericardial effusion had developed and a pericardiocentesis was performed. The helex device and long sheath were removed from the patient; however, the pericardial effusion persisted. Following approximately 4 hours treatment of the effusion, the patient expired."

Conclusion:
No erosion as the pericardial effusion was confirmed to be a procedural complication and the GORE® HELEX® Septal Occluder was not left in the patient.

MDR #2017233-2009-00527 / Gore Event #10808

"It was reported that helex septal occluder was implanted in 2009. Two months later, it was noted that the occluder had embolized to the right ventricular outflow tract. An attempt was made to snare the device three days later, but was unsuccessful. The helex device was successfully retrieved from the right ventricular outflow tract through interventional techniques six days later. During the retrieval, the physician unknowingly crossed the atrial septal defect and perforated the left atrium. The pt went into cardiac tamponade and was converted to open surgery. The pt tolerated the surgery and was doing well following the procedure."

Conclusion:
No erosion as the cardiac tamponade was confirmed to be a procedural complication during transcatheter retrieval of the GORE® HELEX® Septal Occluder.

MDR #2017233-2010-00458 / Gore Event #12785

"It was reported the physician implanted a gore helex septal occluder to close an atrial septal defect. The pt had redundant primum tissue that was slightly aneurysmal and the defect measured between 6 and 7. 7mm on transthoracic echocardiography. No balloon sizing was performed. Upon implant, the device appeared equally deployed and well apposed to the septum. Later that night, the device embolized to the main pulmonary artery. While attempting to retrieve the device with a snare, the main pulmonary artery was perforated and a pericardial effusion developed. The patient was converted to surgery where the perforation was repaired, the occluder removed, and the defect surgically closed. The pt was doing well following the procedure."

Conclusion:
No erosion as the pulmonary artery perforation and pericardial effusion were confirmed to be a procedural complication during transcatheter retrieval of the GORE® HELEX® Septal Occluder and the device was surgically removed without clinical sequelae or evidence of tissue erosion by imaging or operative report.

MDR #2017233-2010-00578 / Gore Event #13289

"It was reported the physician was implanting a 25mm gore helix septal occluder. The defect measured 12mm on fluoroscopy. A 25mm helix device was implanted in the defect. While removing the retrieval cord, it was noted that the right disc of the device had slipped into the defect. The physician attempted to grab the right disc of the device with a snare and forceps but the device embolized to the right iliac

artery. While attempting to retrieve the device with forceps, the iliac artery was perforated. The helix device was forced against the arterial wall by blood flow and could not be captured. A gore viabahn covered stent was deployed to cover the perforation and pin the helix device to the wall of the artery. The patient was doing well following the procedure."

Conclusion:
No erosion as the iliac artery perforation was confirmed to be a procedural complication during attempted retrieval of an embolized GORE® HELEX® Septal Occluder.

MDR #2017233-2008-00924 / Gore Event #7586

"It was reported in 2008, the physician implanted a 30mm helex septal occluder in a female to close an asd (atrial septal defect). The pt had a symptomatic asd and was obese, with dyspnea on exertion. The physician had difficulty gaining access on the right side, so access had to be obtained from the left femoral vein. The pt had bilateral hematomas post procedure. A superficial femoral av fistula on the right side required surgical repair at 30 days. The pt was doing well after the repair."

Conclusion:
No erosion as the superficial femoral AV fistula was not related to the implanted GORE® HELEX® Septal Occluder.

MDR #2017233-2010-00521 / Gore Event #13074

"It was reported the physician was implanting a 25mm gore helex septal occluder on (b)(6)2010, to close an atrial septal defect. During the cardiac catheterization procedure, the pt developed complete heart block. The following day, the heart block persisted and a steroid infusion was administered. On (b)(6) 2010, echocardiography showed a 2-3mm pericardial effusion and the arrhythmia persisted. On (b)(6) 2010, the effusion had reduced in size. The pt was issued a holter monitor, prescribed oral steroids, and discharged from the hospital. Following discharge, holter monitor readings show improved conduction with periods of sinus rhythm and second degree heart block. The pt is currently stable."

Conclusion:
No erosion as the arrhythmia was confirmed to be a procedural complication.

MDR #2017233-2011-00061 / Gore Event #13598

"It was reported the physician implanted a gore helex septal occluder to close an atrial septal defect. At implant, the device appeared in good position and appropriately apposed to the septum. At one month f/u, the physician noted a pericardial effusion. There was no clinical sequela and no tamponade noted. The

physician performed a pericardiocentesis and drained the effusion. The device remains implanted and the pt was doing well following the procedure."

Conclusion:
No erosion as there was no clinical sequelae, no hemodynamic compromise, no tamponade, and no further complications following drainage of the effusion. The pericardial effusion was incidentally noted at the one-month follow-up, and the device remains implanted.

MDR #2017233-2008-00505 / Gore Event #6885

"It was reported that the physician implanted a helex septal occluder in 2008 to close an asd (atrial septal defect). At approximately 6 weeks later, the device was surgically removed for impinging on the mitral valve. A residual leak, frame fracture on the left atrial disc and a punctured mitral valve leaflet were also noted. The mitral valve leaflet was repaired with a single stitch and the defect was surgically closed. The explanted device and images will be returned for examination. The patient was doing well following the procedure."

Conclusion:
No erosion as the GORE® HELEX® Septal Occluder was surgically explanted without clinical sequelae or evidence of tissue erosion by imaging or operative report.

GORE® HELEX® Septal Occluder MDRs in Not ASD (PFO, Other) Applications

Seven (7) of the MDRs occurred in PFO applications and, per the St. Jude erosion algorithm, would be excluded from further analysis as being "off-label". While the St. Jude algorithm would cease erosion evaluation at this point, Gore believes that erosions should be considered in all applications in which the device is used. Therefore, Gore analyzed each of these events and determined that none of them are erosions:

MDR #2017233-2008-00056 / Gore Event #6198

"The physician was implanting a helex septal occluder to close a pfo (patent foramen ovale). The patient had a floppy septum. The physician did not balloon size the pfo, instead he did a trans - septal puncture to create a central defect. A 25mm device was implanted in the pfo defect. Within 24 hours, the device embolized to the descending aorta, where it was found on the follow-up echo. The day after implant, the device was easily removed in a transcatheter procedure. After the device was removed, the physician balloon sized the defect to be 20-22mm. A competitor device was implanted and the patient was doing well."

Conclusion:
No erosion as a GORE® HELEX® Septal Occluder was not left in the patient.

MDR #2017233-2008-00942 / Gore Event #7591

"It was reported that the physician was implanting a helex septal occluder to close an aneurysmal pfo (pt foramen ovale). Ice (intracardiac echocardiography) images were not very helpful in visualizing the device or defect. While forming the right disc the lock prematurely released. While retrieving the device the retrieval cord broke, so a snare was used to remove the device. The physician was using a guide wire and diagnostic catheter when the pt became tachycardic and the blood pressure started to drop. It was discovered using tee (transesophageal echocardiography) that the left atrial appendage had been perforated. The pt was immediately taken to surgery to repair the perforation. The pt was in stable condition following the repair."

Conclusion:
No erosion as a GORE® HELEX® Septal Occluder was not left in the patient and the LAA perforation was confirmed to be a procedural complication.

MDR #2017233-2009-00291 / Gore Event #9576

"It was reported that the physician was implanting a 20mm helex septal occluder to close a pfo (patent foramen ovale). The physician crossed the defect and while forming he left atrial disc, the device prematurely locked. The physician removed the mandrel and attempted to remove the occluder with the retrieval cord. The cord broke; hence a 25mm goose neck snare was used. The physician was unable to snare the device so biotome forceps were used to capture the device and retrieve it into the delivery catheter. A second 25 mm helex device was successfully implanted. Upon evaluation of the patient, the physician noted a pericardial effusion. The physician performed a pericardiocentesis procedure to drain the effusion. The patient was then treated with 20mg of protamine. The patient was stabilized with good vitals and no residual effusion. On follow up, the patient was in good condition."

Conclusion:
No erosion as pericardial effusion was confirmed to be a procedural complication.

MDR #2017233-2010-00166 / Gore Event #11811

"It was reported that the physician implanted a helex septal occluder to close a patent foramen ovale. Four hours post implant, the patient had cardiac tamponade. A pericardiocentesis was performed thereby resolving the tamponade. The patient is doing well."

Additional Information:
In follow-up discussion with the physician, he indicated that the patient had received another company's device implanted in the PFO a week earlier. The patient had a thickened secundum tissue portion of the PFO, which prevented the device from coming to rest flat on the septum. He decided to bring the patient back for a second procedure, remove the previously placed device, and replace it with a GORE® HELEX® Septal Occluder. During the procedure, the first device was difficult to remove and the GORE® HELEX® Septal Occluder was difficult to deploy. The Physician's assessment was that the combination of device removal and difficulties with deployment led to the tamponade. Once the initial adverse events were overcome, the patient continued to do well and the device remained implanted.

Conclusion:
No erosion as the cardiac tamponade was confirmed to be associated with a procedural complication. The GORE® HELEX® Septal Occluder remains implanted and no further clinical sequelae have been reported.

MDR #2017233-2010-00497 / Gore Event #13073

"It was reported that the physician was implanting a gore helex septal occluder to close a pfo (patent foramen ovale). While gaining guidewire access across the pfo, the pt complained of chest pain. The physician then balloon sized the defect and a 30mm helex device was selected. The helex device was implanted in good position with no issues. Before the pt was moved out of the cath lab, he experienced tachycardia and shortness of breath. The pt went into cardiac tamponade on the table, so chest compressions commenced. A pericardial effusion was noted and drained. The pt was taken to surgery and a perforation of the left upper pulmonary vein was noted. The device was evaluated by the surgeon and still noted to be in good position. The device remains implanted and the pt was stable and doing well after the surgery."

Conclusion:
No erosion as the cardiac tamponade was confirmed to be a procedural complication.

MDR #2017233-2010-00577 / Gore Event #13363

"It was reported that the physician was implanting a gore helex septal occluder to close a long tunnel pfo (patent foramen ovale). While balloon sizing, it appeared the sizing balloon was too far in the left atrium and part of it was in the pulmonary vein. The sizing balloon was repositioned and a size of 12mm was reported. A 30mm helex device was prepped and advanced across the pfo. While the left disc was being formed, the pt's blood pressure dropped and a pericardial effusion was noted. The device was removed and a pericardiocentesis was performed. The pt was stable and doing well the next day."

Conclusion:
No erosion as the pericardial effusion was confirmed to be a procedural complication.

MDR #2017233-2009-00370 / Gore Event #10050

"It was reported that in 2007, the physician implanted a helex septal occluder to close a patent foramen ovale (pfo) that balloon sized to 8mm. At 6 and 12 month follow ups, trans thoracic echocardiogram (tte) revealed a shunt inferiorly to the device. In 2009, a trans esophageal echocardiogram (tee) showed a residual shunt across the pfo. The physician performed a transeptal puncture and placed a 30mm occluder, therby closing the defect. The patient was doing well following the procedure."

Conclusion:
No erosion as the reason for re-intervention was a residual shunt and there was no clinical evidence of tissue erosion confirmed through imaging and/or operative reports.

c) Conclusions from Erosions Analysis

The detailed review provided above reaffirms Gore's conclusion that a total of **0 device erosions** of the aortic root or the free wall of the atria have been reported **in over 12 years of clinical experience with an estimated 12,685 to 18,184 devices implanted worldwide**.

3. Risk Mitigators

The design of the GORE® HELEX® Septal Occluder is unique in that the left and right atrial discs are soft and conformable, and does not exert undue force onto the heart. This design feature serves as a primary mitigator of risk for device erosions, and it is Gore's belief that this design characteristic is the leading reason for an absence of erosions associated with the worldwide, all-application use of the device.

Even in the absence of erosions, Gore continues to collect data regarding erosions from its Post Approval Study and worldwide product surveillance.

C. Post-Procedural Device Embolization

1. Description

Post-procedural device embolization is the dislodgement of the occluder from the septum after conclusion of the procedure, and subsequent device migration to the pulmonary or systemic circulation (i.e. the pulmonary artery or the descending aorta).

This event has long been known to be a potential adverse event for transcatheter devices.

2. Occurrence Rate

In the most recent follow-up on the Gore clinical trial patients, 6 post-procedure device embolizations were noted. One device was removed during a subsequent surgical procedure, in which the physician deemed the defect to be best suited for surgical repair (following the embolization). The remaining 5 device embolizations were recovered via a subsequent transcatheter procedure. The defects were then repaired with an alternative transcatheter option and open surgical repair was avoided.

A review of the post-procedural device embolization data from the clinical studies indicates that the occurrence rate differs depending on the nominal size of the device relative to that of the defect. **Table 40** demonstrates that the risk of post procedure device embolization increases as the nominal device diameter to defect diameter ratio decreases. All post procedure device embolizations observed in the US clinical studies occurred in patients in which the nominal device diameter was less than twice that of the balloon sized defect diameter. Balloon sizing of the defect to achieve a 'stop-flow' measure is a mandatory component of all the US clinical studies.

Table 40. Post-Procedure Embolizations By Nominal Device Diameter to Defect Diameter Ratio

	Nominal Device Diameter to Defect Diameter Ratio			
Subjects Retaining Device	**< 1.6 (N=33)**	**1.6 - < 2.0 (N=164)**	**2.0 + (N=228)**	**Overall (N=425)**
Embolization (post- procedure)	1 (3.0%)	5 (3.0%)	-	6 (1.4%)

With regard to the commercial experience of the GORE® HELEX® Septal Occluder, the estimated occurrence rate of post-procedure embolization was less than half the incidence observed in the US clinical studies. Gore believes that the lower rate observed commercially has been positively influenced by the institution of risk mitigators, a discussion of which follows.

3. Risk Mitigators

Patients with post-procedural device embolization generally require a subsequent surgical or transcatheter procedure to recover the GORE® HELEX® Septal Occluder. The device design lessens the severity associated with reintervention. Specifically, the occluder is constructed from a single helical wire and soft ePTFE patch material, allowing the device to be readily elongated and retrieved via a large diameter sheath and a snare. However, not all removals occur by a transcatheter means. Some physicians elect to send patients to surgery once an embolization is experienced, deeming the defect to have been better suited for surgical closure.

In addition to the design of the device, modification of sizing recommendations based on the US clinical trial data has served as a risk mitigator for post procedure device

embolizations. Throughout the US clinical studies, the recommended nominal device diameter to defect diameter sizing ratio was 1.6:1. It was not until an analysis of the clinical study data, however, that the importance of using a 2:1 nominal device diameter to defect diameter sizing ratio to reduce the potential for device embolization was recognized. Accordingly, Gore's recommendations regarding device sizing were changed in 2006 to inform clinicians regarding the best practices associated with the use of the device.

The risk of a post procedure device embolization is mitigated by specific recommendations provided in the product's *Instructions for Use*. These include:

> **a. Warnings (page 2 of IFU):** *The defect should be evaluated to ensure there is an adequate rim to retain the device in ≥ 75% of the circumference of the defect.*
>
> **b. Warnings (page 2 of IFU):** *The selected occluder diameter should be at least two times the diameter of the defect (i.e., a 2:1 ratio of device diameter-to-defect diameter). Deploying the occluder in cases where the occluder diameter-to-defect diameter ratio is below 2:1 increases the risk of unsuccessful device placement and device embolization.*
>
> **c. Recommended procedure (page 3 of IFU):** *Patients should have Transthoracic Echocardiographic (TTE) exams prior to discharge, and at 1, 6, and 12 months after occluder placement to assess defect closure.*

The first recommendation relates to the integrity of the septum itself, instructing physicians to make adequate assessments of the septal defect morphology prior to implantation. The second recommendation incorporates the lessons learned from the clinical studies. The third recommendation allows for early identification of an embolization, should one occur.

The current language within the device's *Instructions for Use* reflects the best practices for reducing the risk of post procedural device embolization, thus helping to ensure successful patient outcomes.

D. Wire Frame Fracture

1. Description

Events requiring reintervention due to wire frame fractures include all events in which it is suspected that the integrity of the occluder, i.e. its ability to maintain appropriate apposition to the septum, is compromised due to a frame fracture. Additionally, removals have been noted to occur in the presence of valve leaflet damage. The mechanism for frame fractures is related to fatigue, and has been hypothesized as stemming from the

repeated ovalization[6] of the device within the atrial chamber. Typically, these fractures occur prior to stabilization of the occluder by tissue in-growth. Outcomes of these events include either transcatheter or surgical removal of the device. **Emergency surgical interventions due to frame fractures have not been reported.**

Frame fractures requiring reintervention, as noted in the GORE® HELEX® Septal Occluder *Instructions for Use*, may be suspected in cases where echocardiography exams indicate a lack of device stability. Fluoroscopic evidence of a frame fracture alone, however, does not warrant a reintervention. Indeed, the independent DSMB from the US clinical studies adjudicated frame fractures without sequelae as minor adverse events, such as shown in **Figure 17.**

Figure 17. Image of a frame facture in a GORE® HELEX® Septal Occluder that does not warrant reintervention (from Fagan, et al. 2009).

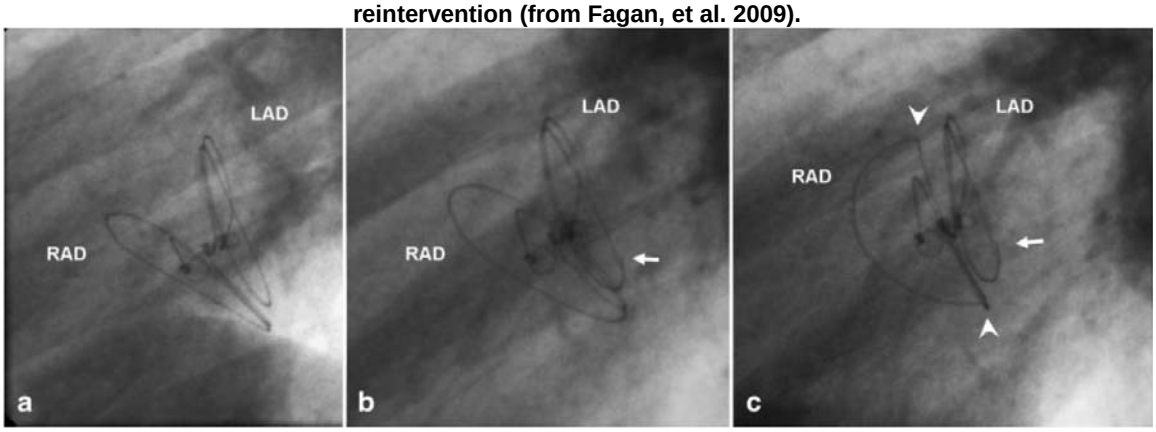

Fig. 2. Fluoroscopic images of a HELEX device shown in an LAO and cranial projection. RAD = right atrial disk; LAD = left atrial disk. (a) Device without WFF at 6 months. (b) WFF of LAD circumferential wire at 18 months indicated by overlap of the fractured ends (arrow). (c) Typical angulated fractures of the RAD (arrowheads) found at 30 months.

2. Occurrence Rates

In the most recent follow-up on the clinical trial patients, 5 devices required reintervention due to wire frame fractures. One device was removed during a subsequent transcatheter procedure, while the remaining 4 were removed during a subsequent surgical procedure. None of these frame fractures required an emergency conversion to surgery. All fractures requiring removal were observed prior to the one-year follow-up. In one instance, the frame fracture was noted early as causing device instability, however it was not removed until >2 years later.

Also noted from the clinical trials, 36 subjects were found with wire frame fractures, i.e. an occurrence rate of 8.3%. Thirty-one of these fractures were deemed as minor adverse events by the independent DSMB, as no harm to the patient was noted and there was no adverse impact to defect closure.

[6] Device ovalization is compression of the device with unequal force around the circumference leading to a slightly oval configuration instead of the intended generally circular configuration.

With regard to the commercial experience with the device, the presence of frame fractures was noted in 14 MDR reports involving the ASD application and 27 reports from the worldwide, all-application experience of the GORE® HELEX® Septal Occluder. No intervention, a subsequent transcatheter procedure, or a subsequent surgical procedure occurred in 22%, 26%, or 52% of cases involving fractures, respectively.

Patients experiencing wire frame fractures requiring device removal have not been observed to be at risk of an emergency surgical procedure. Reinterventions for wire frame fractures have been performed in response to residual shunts and/or excess turbulence in the right or left atrium.

Additionally, within the worldwide, all-application experience of the GORE® HELEX® Septal Occluder, three cases of valvular damage have been noted in patients with wire frame fracture. In each case, the device was in contact with the anterior leaflet of the mitral valve, a situation that the current IFU cautions against. The frame fracture occurred on this contact point yielding valvular damage that warranted surgical repair of the valve leaflet.

Based on these rare, but important adverse events, appropriate device selection/sizing and follow-up are important in reducing the overall risk of reintervention and the prevention of long term clinical sequelae. A discussion of risk mitigators follows.

3. Risk Mitigators

The GORE® HELEX® Septal Occluder was specifically designed to mitigate the risk of a serious adverse event should a frame fracture develop. Specifically, the single wire constituting the frame of the GORE® HELEX® Septal Occluder is almost completely enclosed in the GORE-TEX® ePTFE material, with the exception of the locking loop and eyelets (see **Section II: Device Description**). The ePTFE material used in the design of the device both serves to occlude the defect and prevent the wire portions from embolizing should a fracture develop.

In addition to the design of the device, the risk of a removal due to frame fracture is mitigated by the specific recommendations provided in the device's *Instructions for Use*. These include:

> **a. Warnings – Regarding device deployment (page 2 of IFU):** *The defect and atrial chamber size should be evaluated by Transesophageal Echocardiography (TEE) or Intracardiac Echo (ICE) with color flow Doppler measurement to confirm that there is adequate space to accommodate the selected occluder size without impinging on adjacent cardiac structures (e.g., A-V valves, ostia of the pulmonary veins, coronary sinus, or other critical features); There must be adequate room in the atrial chambers to allow the right and left atrial discs to lie flat against the septum with disc spacing equal to the septal thickness, and without interference with critical cardiac structures or the free wall of the atria.*

b. Precaution – Post-implant (page 3 of IFU): *Patients should have Transthoracic Echocardiographic (TTE) exams prior to discharge, and at 1, 6, and 12 months after occluder placement to assess defect closure. Attention should additionally be given towards the stability of the device during these assessments, as a lack of device stability may be indicative of wire frame fractures. In instances where device stability is questionable, fluoroscopic examination without contrast is recommended in order to identify and assess wire frame fractures.*

c. Recommended procedure (page 11 of IFU): *To assure that there is adequate space to accommodate the disc within the atrial chambers, the selected occluder diameter should be no more than 90% of the measured septal length. Additionally, confirm that there is adequate space to accommodate the selected occluder size without impinging on adjacent cardiac structures (e.g., A-V valves, ostia of the pulmonary veins, coronary sinus).*

The first and third recommendations, above, instructs implanting physicians to ensure that the selected nominal device diameter of the occluder not occupy more than 90% of the septal length with a focus on not impinging adjacent cardiac structures. If a fracture were to occur, adherence to this recommendation should prevent potential damage to adjacent cardiac structures, as the frame would not be in contact with them.

The second recommendation, above, provides clarity to the implanting physician regarding the appropriate post-procedural assessment of patients. Frame fractures, other than those involving device instability, are incidental in nature.

The current language within the device's *Instructions for Use* reflects the best practices for reducing the risk of reintervention due to wire frame fracture, thus helping to ensure successful patient outcomes.

E. Reintervention Due to Residual Shunt

1. Description

The primary efficacy endpoint for atrial septal defect therapy is defect closure and the reduction of the concomitant risks associated with intra atrial shunting. If the closure is not clinically successfully, the risk of stroke or a hemodynamic compromise still exists and the effected patient will require an additional procedure to complete the defect closure. Post-procedural reinterventions due to persistent residual shunt following implantation of a GORE® HELEX® Septal Occluder were assessed within this group of adverse events.

With the GORE® HELEX® Septal Occluder a residual leak requiring reintervention can occur if:

- the nominal device diameter to defect diameter ratio prevents the disc from covering the defect (sizing), or
- the disc does not rest flat upon the septum allowing flow under the circumference of the disc (anatomy), or
- multi-fenestrated septal tissue with numerous small defects exist that permit shunting outside the periphery of the closure device (anatomy).

Residual shunts can be treated by one of two therapies, removal of the device with surgical closure, or a staged transcatheter therapy where multiple devices are placed in the defect(s).

2. Occurrence Rates

Clinically significant residual leaks were reported in 6 subjects within the US clinical studies. None of these subjects were reported to require reintervention, either surgical or transcatheter, due to the residual leak. Of the two patients that were followed for more than 12 months, one patient's residual leak status was changed to clinically insignificant at 36 months while the other is pending follow-up.

Additionally, 3 subjects from the US clinical studies had their devices removed surgically at the 24 hour follow-up window for inappropriate size or malposition. In each case, the primary reason for removal was due to anatomical and sizing constraints (i.e. defect deemed unsuitable for repair with the GORE® HELEX® Septal Occluder).

With regard to the commercial experience with the device, reintervention due to residual shunts or malposition was noted as one of the most frequent adverse events. These occurred at a rate of 0.36% – 0.52% in the ASD application following FDA approval of the device, and 0.42% – 0.60% in the worldwide, all-application use of the device.

The nature of reintervention for residual shunts and malposition, for the ASD application, was a subsequent transcatheter procedure in 52% and a subsequent surgical procedure (for repair of the defect) in 48%. With regard to the worldwide, all-application use of the device, this adverse event warranted a subsequent transcatheter procedure in 58%, a subsequent surgical procedure (for repair of the defect) in 37%, and 5% were continuing to be followed with no intervention yet to be reported.

3. Risk Mitigators

Incomplete closure is typically the result of device size selection and/or the underlying septal anatomy. The device's *Instructions for Use* offer best practice recommendations to help ensure successful placement and retention of the device. Specifically, these recommendations include:

> **a. Warnings – Regarding device deployment (page 2 of IFU):** *The defect and atrial chamber size should be evaluated by Transesophageal Echocardiography (TEE) or Intracardiac Echo (ICE) with color flow Doppler measurement to confirm*

that there is adequate space to accommodate the selected occluder size without impinging on adjacent cardiac structures (e.g., A-V valves, ostia of the pulmonary veins, coronary sinus, or other critical features); There must be adequate room in the atrial chambers to allow the right and left atrial discs to lie flat against the septum with disc spacing equal to the septal thickness, and without interference with critical cardiac structures or the free wall of the atria.

b. Warnings – Post-implant (page 2 of IFU): *The selected occluder diameter should be at least two times the diameter of the defect (i.e., a 2:1 ratio of device diameter-to-defect diameter). Deploying the occluder in cases where the occluder diameter-to-defect diameter ratio is below 2:1 increases the risk of unsuccessful device placement and device embolization.*

c. Precaution – Post-implant (page 3 of IFU): *Patients should have Transthoracic Echocardiographic (TTE) exams prior to discharge, and at 1, 6, and 12 months after occluder placement to assess defect closure. Attention should additionally be given towards the stability of the device during these assessments, as a lack of device stability may be indicative of wire frame fractures. In instances where device stability is questionable, fluoroscopic examination without contrast is recommended in order to identify and assess wire frame fractures.*

d. Recommended procedure (page 11 of IFU): *To assure that there is adequate space to accommodate the disc within the atrial chambers, the selected occluder diameter should be no more than 90% of the measured septal length. Additionally, confirm that there is adequate space to accommodate the selected occluder size without impinging on adjacent cardiac structures (e.g., A-V valves, ostia of the pulmonary veins, coronary sinus).*

The first, second, and fourth recommendations, above, instruct physicians regarding best practices around sizing and device-anatomy interactions. The third recommendation provides clarity to the implanting clinician regarding the appropriate post-procedural assessment of their patients.

The current language within the device's *Instructions for Use* reflects the best practices for reducing the risk of reintervention due to residual shunt or poor apposition, thus helping to ensure successful patient outcomes.

F. Arrhythmia

1. Description

Patient populations requiring treatment for *ostium secundum* atrial septal defect are associated with a small rate of arrhythmias. The presence of an ASD represents an abnormality, which in itself, predisposes the patient to be susceptible to conduction issues (Kutty et al., 2012, see **Attachment 10**). Reports of arrhythmias requiring

ongoing medical or pacemaker therapy following implantation of the GORE® HELEX® Septal Occluder are presented here.

2. Occurrence Rates

Arrhythmias requiring ongoing treatment were assessed within the US clinical studies. The rate of this adverse event is rare, i.e. 0.7% across the four US clinical studies. It is difficult to isolate the reported arrhythmia as a device related issue, or one related to the congenital anomaly itself.

With regard to the commercial experience, the report of arrhythmia requiring ongoing treatment was similarly rare, occurring in 0.13% – 0.19% of ASD patients since FDA approval, and in 0.11% - 0.16% of patients throughout the worldwide, all-application experience of the device.

Additionally, clinical literature assessing new-onset atrial fibrillation (either requiring ongoing treatment or not) following the implantation of septal occluders was presented in a large series publication by Staubach and colleagues (2009). These authors compared the post-procedural occurrence of atrial fibrillation or flutter in a series of 1,349 consecutive PFO patients implanted with various devices. The series included 379 GORE® HELEX® Septal Occluder patients in the review. An ECG was conducted on patients before admission and before discharge, and after one, three, and six months post-procedure.

The incidence rate of atrial fibrillation / flutter was statistically greater with the STARFLEX Device (10%) as compared to various AMPLATZER® occluders (2.9%), the GORE® HELEX® Septal Occluder (1.8%) or the PREMERE PFO Occluder (1.5%). It was postulated that the potential mechanisms of atrial fibrillation following percutaneous closure may include intrinsic patient related factors as well as local stretch or irritation from the device itself.

Although this paper was specific to the application of PFO, it supports the conclusion that the rate of new onset arrhythmia due to the anatomy's interaction with the GORE® HELEX® Septal Occluder is low.

3. Risk Mitigators

The GORE® HELEX® Septal Occluder has been designed to have right and left atrial discs that are both soft and conformable, and is not thought to adversely affect the shape of the surrounding tissue. Its generally circular shape additionally mitigates "pressure points" on the septum, which may otherwise have the potential to cause arrhythmic episodes. Finally, the tissue response elicited by the ePTFE material is benign, and does not instigate exuberant scar formation. Thus, the design of the implantable device is the best mitigator of risk for arrhythmias requiring ongoing treatment.

G. Thrombus

1. Description

Thrombus formation is the procedural or post-procedural identification of an echogenic mass or thrombus on the occluder. Reducing thrombus formation as low as feasible is important in preventing embolic events, such as stroke or transient ischemic attacks or infarcts of the myocardium, kidneys, gastrointestinal tract or peripheral circulation.

2. Occurrence Rate

The occurrence of procedural or post-procedural device thrombosis was rare for the GORE® HELEX® Septal Occluder. This event was not identified within the US clinical studies; however, it was listed as a potential adverse event in the *Instructions for Use* throughout the study. Within the worldwide, all-application commercial experience with the device, thrombus was noted in 7 cases, i.e. an estimated occurrence rate of 0.04% – 0.06%. Of these 7 cases, 1 was resolved via medical therapy, 2 via a transcatheter intervention, and 4 via surgical intervention. Details regarding procedural anticoagulation and/or follow-up antiplatelet/anticoagulant therapy were unknown. There were also two incidents of procedural stroke/TIA reported in the world wide commercial experience (incidence less than 0.02%). Although both these events occurred during the transcatheter procedure, a direct relationship to the occluder cannot be ruled out in this retrospective review.

3. Risk Mitigators

The design of the GORE® HELEX® Septal Occluder serves as a primary mitigator for the risk of thrombus formation. The device is constructed of ePTFE, a well known biologically inert, minimally thrombogenic biomaterial. Greater than 90% of the wire frame is encased in this material. Gore attributes the low rate of thrombus formation to this design attribute.

Additionally, physicians implanting the device are instructed within the device's *Instructions for Use* regarding best practices regarding thrombus. These include:

> **a. Precautions – Procedural (page 2 of IFU):** *Patients should be heparinized sufficiently to maintain an Activated Clotting Time (ACT) greater than 200 seconds throughout the procedure.*
>
> **b. Precaution – Post-implant (page 2 of IFU):** *Patients should be treated with antiplatelet therapy, such as aspirin or clopridogrel bisulfate, for six months post-implant. During the Pivotal and Continued Access Clinical Trials, 68.4% of device patients received antiplatelet medications and 0.9% received anticoagulants for up to six months post-procedure. The decision to continue antiplatelet therapy beyond six months is at the discretion of the physician.*

Both of the recommendations listed above are consistent with similar transcatheter procedures, and reflect best practices for the mitigation of procedural or post-procedural device thrombosis.

H. Other

Serious adverse events, other than those listed above, occur rarely, i.e. less than 0.02%. These "Other" adverse events include, nickel allergy, infection, procedural strokes/TIAs, air embolism, etc.

The GORE® HELEX® Septal Occluder has been designed to mitigate the risks of these rare events, where possible, but a complete absence of procedural complications, infection, and/or allergy cannot be attained. A review of the low occurrence rate of these other risks demonstrate the GORE® HELEX® Septal Occluder to be a viable treatment option for patients requiring repair of *ostium secundum* atrial septal defects.

I. Safety Conclusions

Gore's data from both clinical trials and the world wide commercial experience reflects low, stable and predictable adverse event rates for the GORE® HELEX® Septal Occluder used in ASD closure. These data predict that approximately 1.04% - 1.50% of patients will experience a serious adverse event.
Serious adverse events occur at a relatively low rate, and most can be treated with minimally invasive techniques. In the event an open surgical repair is required to treat an adverse event, such procedures have a long, reliable history of ASD repair.

This safety profile, coupled with the effectiveness of the device in closing the underlying defect without trauma and scarring, while allowing patients to promptly return to activities of daily living, demonstrate the clinical utility of the GORE® HELEX® Septal Occluder.

VI. REVIEW OF PUBLISHED LITERATURE

A. Introduction and Background

Within this section, an overview of published literature demonstrating the safety and performance of the GORE® HELEX® Septal Occluder is presented. Clinical publications presented in this review demonstrate that the GORE® HELEX® Septal Occluder has a similar risk profile compared to alternative techniques and products used for the same applications. Additionally, the history of satisfactory use and low complication rates establish that when used as indicated, the GORE® HELEX® Septal Occluder achieves the safety and performance requirements claimed by Gore.

B. Methodology, Objective, and Scope of the Review

Peer-reviewed journal articles referencing the use of the GORE® HELEX® Septal Occluder are included in this literature review. Case studies and publications reporting on less than 10 patients receiving the GORE® HELEX® Septal Occluder were excluded unless these articles highlighted events that were not represented in the other articles. The types of studies that are relevant to this objective are specified and the extents to which the scientific articles relate to the device in question and its limits are shown.

Publications referenced in this review include a variety of applications and clinical endpoints. Both applications regarding the transcatheter closure of *ostium secundum* atrial septal defects and that of patent foramen ovale are detailed. Performance metrics such as defect closure, thrombus formation, device embolization, recurrent neurological events, any other adverse event, and clinical success are summarized here. To the best of Gore's knowledge all adverse events in the literature are accounted for in the clinical trial data or the MDR reporting (MAUDE database).

C. Results of Literature Review

The publications identified in this are categorized according to the defect type in which the GORE® HELEX® Septal Occluder was used, i.e., ASD and/or PFO. A high level overview of the extracted articles is provided in **Table 41**. Furthermore, detailed summaries of each article are provided in **Attachment 11: Literature Review.**

Table 41. Summary of Clinical Literature

Citation	Application	GORE® HELEX® Patients	Notes
Vincent, et al., 2003	ASD	14	- 13/14 patients had successful closure - Report of nickel allergy in one patient
Lopez, et al., 2003	ASD	49	- 94% rate of successful closure - No case of residual right ventricular volume overload upon follow-up
Latson, et al., 2006	ASD	342	- 87% of patients where a device implantation was attempted received successful closure - Major adverse event occurred in 5.8%
Jones, et al., 2007	ASD	119	- Comparison of device closure to surgical closure - Device closure was not inferior to surgical closure
El-Sisi, et al., 2008	ASD	12	- No reports complications attributed to the device - Complete closure reported in 11 patients at one-month follow-up; the remaining patient had a trivial to mild residual leak
Smith et al., 2008	ASD	33	- Mid-term (~5 year) follow-up of first 33 patients to receive the GORE® HELEX® Septal Occluder - No significant ECG, hemodynamic, sequelae - No symptoms of thromboembolism, infection, or endocarditis
Fagan et al., 2009	ASD	298	- 6.4% rate of wire frame fractures - No clinical sequelae, except for one device being percutaneously removed 6 weeks post implant due to lock loop fracture
Quereshi, et al., 2009	ASD	1	- Case report describing unique case of valve perforation due to an early wire frame fracture
Sievert, et al., 2001	PFO	33	- No recurrent embolic events
Onorato, et al., 2003	PFO	4	- No recurrent embolic events - 1 report of cardiac tamponade
Wahl, et al., 2005	PFO	20	- No recurrent embolic events - 95% of patients had closure at follow-up
Billinger, et al., 2006	PFO	128	- Residual shunt resolved completely in 90% of patients - One recurrent TIA, although in a patient with a closed PFO
Ponnuthurai, et al., 2008	PFO	68	- No adverse events reported - Complete closure in 95.6% of patients at 3-month follow-up
Taaffe et al., 2008	PFO	220	- Closure rate of 41.8% immediately post procedure, and 52.7% at 30 days follow-up - Complications with the GORE® HELEX® Septal Occluder were fewer than those with the NMT device and less serious than the AMPLATZER® device
von Bardeleben, et al., 2008	PFO	110	- The GORE® HELEX® Septal Occluder is slower to attain complete closure than either the AMPLATZER® devices or the NMT device - Complete closure is attainable over time,

Citation	Application	GORE® HELEX® Patients	Notes
			and was reported at 100% after 2 years - No recurrent cerebral embolic events reported (one migraine was reported) - No reports of thrombus formation
Scott, et al., 2009	PFO	1	- Case report describing unique case of lock loop fracture identified 3 months post implant
Staubach, et al., 2009	PFO	379	- Paper comparing frequency of new onset atrial fibrillation in patients implanted with various PFO occluders - The GORE® HELEX® Septal Occluder demonstrated a new onset atrial fibrillation in 1.8% of the patients, this compares to a 10% occurrence rate in STARFlex patients, a 2.9% in AMPLATZER® occluder patients, and 1.5% in St. Jude Premere patients
Majunke, et al., 2010	PFO	404	- Discussion of the safety / efficacy of implanting multiple devices in a single patient - 18 patients, originally implanted with a GORE® HELEX® Septal Occluder, were referred to the center for percutaneous closure of a residual leak - A 94% success rate was noted in this procedure
Hammerstingl, et al., 2011	PFO	23	- No recurrent embolic events - 65% of patients had closure at 24 month follow-up
Siddiqui, et al., 2011	PFO	23	- 65% of GORE® HELEX® Septal Occluder Cases utilized Fluoroscopy only - No procedural complications in the GORE® HELEX® Septal Occluder group - 93% of patients had closure at 6 month follow-up
Sorensen, et al. 2011	PFO	315	- Assessment of residual shunt utilizing TCD at 3 months post procedure - 93% closure rate noted with the GORE® HELEX® Septal Occluder at the 3 month follow-up - 35% of the leaking patients at three months were shown to have complete closure at 6 months
Thaman, et al., 2011	PFO	48	- Large residual leaks noted in 45.8% of patients at 6 month follow-up - Large residual leaks noted in 25% of patients at final follow-up
Verma, et al. 2011	PFO	1201	- Characterization of reasons for device explantations at 18 institutions over the last 9 years - 2 GORE® HELEX® Septal Occluder explants were noted of 1201 devices implanted, i.e. 0.17% removal rate
Latson, et al., 2000	ASD / PFO	19 / 9	- Complete echocardiographic closure in 93% of patients within 1 month
Pedra, et al., 2003	ASD / PFO	7 / 3	- 100% successful implantation - After 1 month, 2 patients with ASDs

Citation	Application	GORE® HELEX® Patients	Notes
			experienced trivial residual shunts
Krumsdorf, et al., 2004	ASD / PFO	123	- Thrombus formation rate of 0.8% - No reported adverse events
Kozlik-Feldmann, et al., 2006	ASD / PFO	10 / 1	- 91% of patients had an immediate occlusion of the defect - No reported adverse events

This literature review details the performance of the GORE® HELEX® Septal Occluder when used for transcatheter septal occlusion of *ostium secundum* atrial septal defects and patent foramen ovale. Device related adverse events identified through this review were consistent with those identified in the ASD clinical studies and worldwide commercial experience. No new adverse events were identified in this review which were not captured by the analysis of clinical and commercial experience. The current labeling reflects each of the identified potential adverse events, as noted in the product's *Instructions for Use*. Post-market information remains consistent and no new or different risks to the patient have been identified.

D. Summary

The GORE® HELEX® Septal Occluder has been available for clinical use outside the United States (OUS) since mid-1999. In the US, the device was commercially approved for distribution in August 2006. Throughout both the 5+ years of US and 12+ years of OUS experience, the GORE® HELEX® Septal Occluder continues to demonstrate a positive risk/benefit profile reaffirming its safety and efficacy for the closure of *ostium secundum* atrial septal defects.

Noteworthy, ***no late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any events requiring late emergency device-related surgical intervention***. Additionally, the majority of major adverse events identified did not require surgical intervention to assist in the event's resolution. Medical Device Reports, physician reported patient outcomes, and peer-reviewed publications continue to affirm the positive risk/benefit ratio associated with the use of the GORE® HELEX® Septal Occluder.

VII. PHYSICIAN TRAINING

A. Program Overview

The physician at a given site must complete a training program (reviewed and approved by FDA), prior to the institution having unrestricted access to the GORE® HELEX® Septal Occluder. The training program for the device is comprised of three parts; a physician training manual slide set to review the device indications and applications, a hands-on *in vitro* training to develop device handling skills, and clinical use of the device under the guidance of a physician proctor or a trained Gore Clinical Specialist Associate.

1. Physician Training Manual
    - Indications for use
    - Occluder and delivery system design
    - Required equipment
    - Summary of clinical trial results

2. *In vitro* device handling skills
    - Deployment in cardiac model
    - Repositioning
    - Lock release
    - Routine un-locking and Occluder removal

3. Clinical use of the GORE® HELEX® Septal Occluder
    - Under Guidance/Technical support, for up to five (5) clinical cases.
    - Guidance/Technical support will be provided by either a Physician Proctor skilled in the clinical use of the GORE® HELEX® Septal Occluder or a Gore Clinical Specialist Associate trained to support the clinical use of the GORE® HELEX® Septal Occluder

Physician training records are maintained by W.L. Gore & Associates, Inc., and confirmation of physician training is made prior to the commercial distribution of product to the physician's institution.

B. Supporting Materials

Training materials have been developed to help achieve the requirements of the physician training program described above. Training is facilitated by the Physician Training Manual. It is intended as a key resource to the physician to provide information on the device and deployment considerations. This presentation reviews the device's indications for use, the occluder and delivery system design and function, provides a listing of required equipment necessary for use with the device, and a summary of the clinical trial results for the device. All physicians must review this presentation prior to having access to the device; it contains a thorough review of the features and benefits of the device.

Also available is a **Deployment Instructions Card** which provides a pictorial, step-by-step guide to the deployment of the device. This information is also available on other pieces including a **Wall Chart**. A copy of the Clinician Training Manual is provided in **Attachment 4.**

As described above, all potential users of the device will receive an *in vitro* training on the device. This training includes the use of either a functional or glued demo GORE® HELEX® Septal Occluder within a heart model to enhance device handling skills through the deployment, repositioning, lock release, and routine un-locking and removal of the occluder. The demonstration and heart model are packaged together in a Physician Training kit.

VIII. LABELING

A. Overview

Gore provides physicians and patients with information to support the safe and effective use of the device. A summary of product labeling and other relevant materials currently available for distribution is provided within this section and referenced appendices. Specifically, discussed are the *Instructions for Use* and patient education/awareness materials.

B. *Instructions for Use*

Gore updates its *Instructions for Use* to reflect the company's current understanding of the device, and the potential adverse events that may be associated with its usage. The current version of the GORE® HELEX® Septal Occluder *Instructions for Use* (IFU), updated in January, 2011, includes a full listing of the device's indications, contraindications, warnings, and precautions. The IFU is provided in **Attachment 3** of this document.

The IFU details the results of the Feasibility, Pivotal, and Continued Access studies required for the commercial approval of the GORE® HELEX® Septal Occluder. These data are complemented with a listing of potential device or procedure-related adverse events that may be associated with the closure of an *ostium secundum* atrial septal defect with the GORE® HELEX® Septal Occluder. Specifically, adverse events associated with the use of the GORE® HELEX® Septal Occluder may include, but are not limited to:

- Repeat procedure to the septal defect
- Device embolization
- New arrhythmia requiring treatment
- Intervention for device failure or ineffectiveness
- Access site complications requiring surgery, interventional procedure, transfusion, or prescription medication
- Thrombosis or thromboembolic event resulting in clinical sequelae
- Impingement on, damage to, or perforation of a cardiovascular structure by the device
- Device fracture resulting in clinical sequelae or surgical intervention
- Air embolism
- Myocardial infarction
- Pericardial tamponade
- Cardiac arrest
- Renal failure
- Sepsis
- Significant pleural or pericardial effusion requiring drainage
- Significant bleeding
- Endocarditis

- Headache or migraine
- TIA or stroke
- Death
- Nickel allergy or sensitivity

In addition, the IFU provides details regarding the best practices for the successful device selection, sizing, and deployment of the GORE® HELEX® Septal Occluder.

C. Changes to *Instructions for Use*

Relevant changes to the recommendations in the *Instructions for Use* (IFU) for the GORE® HELEX® Septal Occluder have occurred since the device was first used clinically. A selection of these changes is noted in **Table 42**, and was implemented as new clinical information became available regarding the use of the GORE® HELEX® Septal Occluder:

Table 42. Notable IFU Changes

Date	Description of Change	Reason for Change
Circa 2006	Change to GORE® HELEX® Septal Occluder ***sizing recommendations***: Previous sizing recommendation was to utilize a nominal device diameter that was 1.6 times greater than that of the balloon sized defect diameter Change was implemented to alter the sizing recommendation to a 2:1 nominal device diameter to defect diameter ratio	Patients receiving a device whose nominal diameter is less than twice that of the balloon sized defect diameter may be at a greater risk for device embolization and residual leaks.
Circa January 2011	Inclusion of ***Frame Fracture Information***: Previous versions of the *Instructions for Use* mentioned "Device fracture resulting in a clinical sequelae or surgical intervention" as a potential adverse event. New version of the IFU added a section describing Gore's understanding, based on clinical study and commercial experience, regarding frame fractures, their occurrence rate, and the incidence of events involving clinical sequelae.	Updated clinical trial data was incorporated to include the complete 1-year results for the Feasibility, Pivotal, and Continued Access Studies. This assessment yielded additional information on the frequency of frame fractures. Additionally, commercial experience yielded some events involving device removal due to frame fracture and other clinical sequelae, and the rate of these events was disclosed.
	Previous versions of the *Instructions for Use* noted that patients implanted with 35 mm devices should be brought back for a 1-year fluoroscopy exam to identify and assess the device. Current language specifies that device apposition is best assessed by echocardiography and that fluoroscopy is only recommended in cases where device stability is questionable.	Device stability, as noted by echocardiography, was a better indicator regarding the appropriateness of a device's position. Fluoroscopy did not alone provide information that could assist interpretation of follow-up images.

As demonstrated above, clinician feedback and clinical data have driven changes to the design and usage recommendations of the GORE® HELEX® Septal Occluder. The current labeling, as detailed in the product's *Instructions for Use,* reflects Gore's current understanding regarding the performance and operation of the device.

D. Patient Education/Awareness

For many patients, atrial septal defects and their treatment are foreign concepts, even after diagnosis of the problem. In most cases, patients receive an initial consult from a physician. However, even with this preliminary discussion, patients and their families will often conduct their own research on this condition and its treatment.

The **Patient Brochure** is provided to physicians to give patients and their families an overview of atrial septal defects. Additionally, the brochure presents information on the transcatheter closure of ASDs with the GORE® HELEX® Septal Occluder, as well as the risks and benefits of the procedure. The intent of the brochure is to supply patients and their families with the information needed to make an informed decision when electing to have this procedure, and contains a web address with reference to the device's *Instructions for Use*.

IX. SUMMARY OF KEY POINTS AND CONCLUSIONS

The GORE® HELEX® Septal Occluder is effective at closing atrial septal defects and the adverse event rate experienced by patients is low, predictable, and stable over time. With a high rate of clinical success, patients treated with the GORE® HELEX® Septal Occluder avoid the trauma and scarring associated with open surgical repair, as well as the extended hospital stay that surgical repair requires. Use of the GORE® HELEX® Septal Occluder does not create additional risk if reintervention is required.

The clinical studies and worldwide clinical experiences with the GORE® HELEX® Septal Occluder reflect the following:

- >98% of patients receiving the device achieve clinically successful occlusion of their defect by the 12 month follow-up.
- Clinical data indicate there is no difference in risk of major adverse event by age.
- ***No late adverse events have been identified that caused hemodynamic compromise requiring emergency surgical intervention, i.e. erosions, or any device related events requiring late emergency device-related surgical intervention.***
- Nominal device diameter to defect diameter ratio (i.e., device sizing) is important for clinical success. The device may embolize if not correctly sized.
- Adverse events resulting from use of the GORE® HELEX® Septal Occluder are infrequent and well understood, and can be managed to provide clinical success for the patient.
- The majority of major adverse events encountered in conjunction with the use of the GORE® HELEX® Septal Occluder can be managed via a second catheterization procedure, especially so if the adverse event is identified early. Early discovery and identification can minimize the need for surgical intervention.
- Few new major occluder-related adverse events have appeared since the clinical trials, and all are appropriately documented in the device's *Instructions for Use.*
- When utilized according to its *Instructions for Use*, the GORE® HELEX® Septal Occluder offers a safe and effective treatment option for patients with *ostium secundum* atrial septal defects.

The data summarized in this document, and the changes made to the device over its history, reflect Gore's commitment to product stewardship. Gore's quality systems, including adverse event reporting, ensure that as understanding of device performance evolves, Gore makes timely modifications to the device, its labeling, or clinician training necessary to maintain the safe and effective use of the device.

Gore's data from both clinical studies and the world wide commercial experience reflect low, stable, and predictable adverse event rates for the GORE® HELEX® Septal Occluder used in ASD closure. These data predict that <2% of patients will experience an adverse event requiring intervention. This safety profile, coupled with the effectiveness of the device in closing the underlying defect, with minimal trauma and scarring, and allowing patients to

promptly return to activities of daily living, demonstrate the safety and efficacy of the GORE® HELEX® Septal Occluder for patients.

Patients and their families tend to prefer transcatheter closure whenever possible. This motivation is fully supported by the clinical data underlying the safety and effectiveness of the GORE® HELEX® Septal Occluder. It is further driven by the desire of patients and families to receive successful treatment through a minimally invasive procedure. The clinical data on the GORE® HELEX® Septal Occluder continues to reflect its safe and effective clinical performance; and its clinical history reveals ***no late adverse events that cause hemodynamic compromise requiring emergency surgical intervention, i.e., erosions***, ***or any events requiring late emergency device-related surgical intervention***. Thus, the GORE® HELEX® Septal Occluder continues to provide patients a safe and effective treatment option that may be selected with the guidance of their treating clinician.