



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: February 15, 2000 0050 '00 FEB 16 P1:49
From: Humanitarian Device Exemptions (HDE) Staff, ODE, CDRH
(HFZ-403)
Subject: HDE Approval Package (H990011)
To: Dockets Management Branch (HFA-305)

Attention:

Lyle Jaffe
Jennie Butler
Gloria Ortega

The following HDE application was recently approved:

HDE Number: H990011
Docket Number: 00M-0599
Device Name: CardioSEAL® Septal Occlusion System
Applicant: Nitinol Medical Technologies, Inc.

Attached is the following information for this HDE:

Approval Order
Summary of Safety and Probable Benefit
Labeling

If you have any questions, please call me at (301)594-1190
ext. 107.

Marsha Melvin
Marsha Melvin

Attachments

00M-0599

AAV 1

APPROVAL ORDER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB - 1 2000

Ms. Sherrie Coval-Goldsmith
V.P. Regulatory Affairs
Nitinol Medical Technologies, Inc.
27 Wormwood Street
Boston, MA 02210

Re: H990011
CardioSEAL® Septal Occlusion System
Filed: October 27, 1999
Amended: December 13, 1999 and January 13 and 31, 2000

Dear Ms. Coval-Goldsmith:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the CardioSEAL® Septal Occlusion System. This device is indicated for closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy. CDRH is pleased to inform you that your HDE is approved subject to the conditions described below and in the enclosed "Conditions of Approval." You may begin commercial distribution of the device after you have submitted an amendment to this HDE with copies of the approved labeling in final printed form.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)). In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as (1) the labeling shall specify the training requirements for practitioners who may use the device as approved in this order and (2) the sale, distribution, and use must not violate sections 502(q) and (r) of the act (21 U.S.C. 352(q) and (r)).

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

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CDRH will notify the public of its decision to approve your HDE by making available a summary of the safety and probable benefit of the device upon which the approval was based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/cdrh/ode/hdeinfo.html>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the HDE number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this HDE submission with copies of all approved labeling in final printed form. As part of our reengineering effort, the Office of Device Evaluation is piloting a new process for review of final printed labeling. The labeling will not routinely be reviewed by FDA staff when HDE applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment. Please see the CDRH Pilot for Review of Final Printed Labeling document at <http://www.fda.gov/cdrh/pmat/pilotpmat.html> for further details.

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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If you have any questions concerning this approval order, please contact
Judy Danielson at (301) 443-8243.

Sincerely yours,

Kimber Richter

Kimber Richter, M.D.
Deputy Director for Clinical
and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.108 of the Humanitarian Device Exemption regulation. The review timeframe for HDE supplements is 75 days except for those submitted under 21 CFR 814.39(e).

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

- 1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or
- 2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but

not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126.

A. ANNUAL REPORT

Annual reports should be submitted at intervals of 1 year from the date of approval of the original HDE. Reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement. Three copies identified as "Annual Report" and bearing the applicable HDE reference number are to be submitted to the HDE Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Reports should indicate the beginning and ending date of the period covered by the report and include the following information required by 21 CFR 814.126(b)(1):

1. An update of the information required under §814.102(a) in a separately bound volume;
2. An update of the information required under §814.104(b)(2), (b)(3), and (b)(5);
3. The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;
4. Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and
5. A summary of any changes made to the device in accordance with supplements submitted under §814.108 and any changes required to be reported to FDA under §814.39(b).

B. ADVERSE REACTION AND DEVICE DEFECT REPORTING

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

- (1) A mixup of the device or its labeling with another article.
- (2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and
 - (a) has not been addressed by the device's labeling or
 - (b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

- (3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Annual Report" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

C. **REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION**

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on April 11, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

- (1) may have caused or contributed to a death or serious injury; or
- (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to Food and Drug Administration, Center for Devices and Radiological Health, Medical Device Reporting, PO Box 3002, Rockville, Maryland 20847-3002. For questions regarding the MDR regulation, please call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and FDA publications, entitled "An Overview of the Medical

Device Reporting Regulation" and "Medical Device Reporting for Manufacturers," are available on the CDRH WWW Home Page (<http://www.fda.gov/cdrh>), through CDRH's Fact-on-Demand (FOD) at 800-899-0381 (FOD # 336, 1336, 509 and 987) or by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Lane
Rockville, Maryland 20850

SUMMARY OF SAFETY AND
PROBABLE BENEFIT

**CardioSEAL® Septal Occlusion System
Summary of Safety and Probable Benefit**

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SUMMARY OF SAFETY AND PROBABLE BENEFIT

1. General Information

Device Generic Name: Transcatheter Cardiac Occlusion Device

Device Trade Name: CardioSEAL® Septal Occlusion System

Applicant's Name and Address: Nitinol Medical Technologies, Inc.
27 Wormwood Street
Boston, Mass. 02210

Humanitarian Device Exemption (HDE) Number: H990011

Date of Humanitarian Use Device Designation: August 4, 1999

Date of Panel Recommendation: Not Applicable (Refer to Section 12 for discussion)

Date of Good Manufacturing Practices Inspection: May 27, 1999

Date of Notice to the applicant: February 1, 2000

2. Indications for Use

The CardioSEAL Septal Occlusion System is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

The CardioSEAL Septal Occlusion System is indicated for the closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.

Cryptogenic stroke is defined as a stroke occurring in the absence of potential phanerogenic cardiac, pulmonary, vascular or neurological sources. Conventional drug therapy is defined as a therapeutic INR on oral anticoagulants.

The effectiveness of this device in this indication has not been demonstrated.

3. Device Description

The CardioSEAL Septal Occlusion System consists of two primary components:

- The CardioSEAL, which is constructed of a metal (MP35N) framework to which polyester fabric is attached, and

- The Delivery Catheter, a coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the CardioSEAL to the defect.

4. Contraindications

Presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained.

Active endocarditis, or other infections producing a bacteremia.

Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate size sheath.

Patients whose defect is too small to allow the 11 F sheath to cross the defect.

Anatomy in which the CardioSEAL size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.

Patients with coagulation disorders who are unable to take antiplatelet or, anticoagulant therapy.

Patients with known hypercoagulable states.

Patients with an intra-cardiac mass or vegetation.

5. Warnings and Precautions:

See Warnings and Precautions in the final labeling (Information for Use).

6. ADVERSE EVENTS

6.1 Observed Adverse Events:

In a 292 patient multi-center High Risk study, 35 patients underwent closure of a PFO to prevent neurological injury. Six (6) patients had failed conventional drug therapy as evidenced by a recurrent stroke and 29 were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy (9); a medical or occupational contraindication to anticoagulation (17); could not tolerate anticoagulation (2); and presence of a thrombus in the right atrium (1).

One patient died of lung cancer while in the study. Eighteen (18) patients have completed a 12 month follow-up visit and five patients completed a 24 month visit.

A total of 44 adverse events were recorded among the 35 patients enrolled in the study for closure of their PFO. These adverse events were classified as Serious (4), Moderately

Serious (16), Not Serious (23), or Unknown Seriousness (1) and were linked to either the device, the implant procedure, the catheterization procedure, or other causes, such as a pre-existing condition. Of these 44 adverse events, 7 events were definitely, probably or possibly related to the device, the implant procedure, or the catheterization. All 7 of these events were classified as moderately serious (Table 1).

Adverse Events – Table 1		PFO (n=35)
	Moderately Serious	
	Early Event*	Late Event**
Device Related		
Transient Neurological symptoms	2	0
Implant Procedure Related		
None	0	0
Catheterization Procedure Related		
ST elevation	1	0
Brachial plexus injury	1	0
Rash	1	0
Pseudoaneurysm at vascular access site	1	0
Tachycardia	1	0

* = Early event is ≤ 30 days from implant. Total =1 early event.

** = Late event is > 30 days from implant. Total =0 late events.

In this study, fractures of the framework have been reported in 9 out of 35 implanted patients. The risk of fracture appears to be related to the size of the Occluder selected relative to the size of the heart chamber. There have been two reports of palpitations which were considered possibly related to device arm fracture. In both cases, they were classified as not serious.

6.2 Potential Adverse Events:

Placement of the CardioSEAL involves using standard interventional cardiac catheterization techniques. Complications commonly associated with these procedures include, but are not limited to:

- Air Embolus
- Allergic dye reaction
- Anesthesia reactions
- Apnea
- Arrhythmia
- Death
- Fever
- Headache / Migraines
- Hematoma and/or Pseudoaneurysm including blood loss requiring transfusion

Hypertension; Hypotension
Infection including Endocarditis
Perforation of Vessel or Myocardium
Stroke / Transient Ischemic Attack
Thromboembolic events
Valvular regurgitation.

6.3 Observed Device Malfunctions:

There were no reports of device malfunctions in this PFO population. However, there were 4 device malfunctions in a supporting cohort of patients with atrial level defects. These malfunctions included: one report of a kink in the delivery system, identified during the device placement; one report of a difficult release, the device was subsequently not used; one report of a device which did not open and the device was subsequently not used; and one report of difficulty advancing the device through the pod resulting from the physician modifying the delivery system. There were no clinical sequelae associated with any of these device malfunctions.

7. Alternative Practices and Procedures

Alternative treatments for PFO's that have failed conventional drug therapy include surgical closure.

8. Marketing History

The CardioSEAL Septal Occlusion System has received the CE mark for marketing in Europe. Since 1997 approximately 1600 devices have been sold in the European Community, Latin America, and certain Pacific Rim countries. The CardioSEAL has been used for the treatment of a variety of defects including VSDs.

The CardioSEAL has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

9. Summary of Preclinical Studies

9.1 Biocompatibility Testing

Biocompatibility testing of the implant and delivery system was shown to be acceptable by the following tests which were performed in accordance with the provisions of the ISO 10993-1 and Good Laboratory Practice (GLP) Regulations, 21 CFR 58:

Hemolysis	Cytotoxicity
Systemic Toxicity	Pyrogenicity
Intracutaneous Toxicity	Sensitization

Additional testing of the CardioSEAL included a 7-day Muscle Implant test and an Ames Mutagenicity Assay. The delivery system was also tested for Thromboresistance, Coagulation: Plasma Recalcification Time and Complement Activation. The results of this additional testing found that the implant material was non-toxic and non-mutagenic and the delivery system material was non-thrombogenic and does not activate complement.

9.2 Bench Testing

9.2.1 CardioSEAL – Bench Testing

1. Chemical analysis – MP35N wire

A chemical analysis was conducted to verify the material composition for all of the components of the permanent implant, specifically the MP35n, polyester fabric, solder, polyester suture, and platinum wire. All of these materials were tested and met their raw material specifications.

2. Mechanical Properties – MP35N wire

Testing was conducted to determine conformance of the MP35N wire to specifications and the corrosion resistance of the wire.

a) Tensile strength/Elongation

Tensile strength and elongation was tested on 124 MP35N wire samples (60 as received and 64 annealed). All samples met the specifications for these characteristics.

b) Corrosion Resistance

To evaluate the susceptibility of the CardioSEAL to stress corrosion cracking, 27 spring arm subassemblies were subjected to static deflections in simulated body fluids. Nine samples were exposed to these conditions out to 6, 9 and 12 months. Scanning electron microscope analysis of the test samples found no evidence of stress corrosion cracking after an exposure of up to 12 months.

3. Mechanical Testing – CardioSEAL

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL is provided in Table 2.

Table 2: Summary of CardioSEAL Testing

<i>Test</i>	<i>Samples Tested</i>	<i>Specification</i>	<i>Results</i>
Fatigue Testing:			
Accelerated Life Testing (Springarm)	N=48 (40mm)	Must withstand 10 yrs. Equivalent (pediatric heart rate) of <i>in vitro</i> fatigue cycle testing with no fractures.	No fractures occurred in 630 million cycles.
Other Mechanical Testing:			
Arm/Body Joint Strength	N= 14	10 lbs min	Mean = 25.66lbs S.D. 2.02lbs
Ball/Body Joint Strength	N=21	8 lbs min	Mean = 10.21lbs S.D. = 0.74lbs
Arm/Fabric Strength	N=30	1 lb min	Mean = 4.23lbs S.D. 0.70lbs
Dislodgement Resistance	N=10 (17mm) N=20 (40mm)	Force required to pull an occluder out of a circular hole (50% of the size of the occluder) must be 38 grams minimum.	17mm = Mean = 169.7g S.D. 13.07g 40mm= Mean = 54.10g S.D. = 3.70g
MRI Compatibility			
MRI Compatible	5 Implants	MR safe up to 1.5 Tesla	Non-ferromagnetic Generated artifact < the size of the implant with 1.5 Tesla

A finite element analysis (FEA) was also performed to compare the springback of the model with the laboratory springback testing, determine the stresses (static and dynamic) during the loading cycle and deployment, and compare the model's fatigue prediction with spring arm fatigue test data.

9.2.2 Delivery Catheter - Bench Testing

To demonstrate the strength of the bonded joints and their ability to resist failure, tensile testing was performed on a minimum of 10 samples for each of the bonded locations. The results found that the strength of each of the bonded joints exceeded the test specification.

9.2.3 CardioSEAL Septal Occlusion System - Bench Testing

A summary of the bench testing conducted to evaluate the performance of the CardioSEAL occluder loaded on the delivery catheter is provided in Table 3.

Table 3: Summary of CardioSEAL Septal Occlusion System Testing

<i>Test</i>	<i>Samples Tested</i>	<i>Specification</i>	<i>Results</i>
Load and Deployment			
Minimum Side Length	17mm N=136	17mm: 10.4 mm min.	17mm: Mean= 2.54mm S.D.=0.61mm
	23mm N=88	23mm: 14.0 mm min.	23mm: Mean= 16.42mm S.D. = 0.55mm
	40mm N=120	40mm: 24.4mm min.	40mm: Mean=27.98mm S.D.=0.69mm
Force into Loader	17mm N=17	5 lbs max (applies to all sizes)	17mm: Mean = 0.93lbs S.D. = 0.35lbs
	23mm N=11		23mm: Mean = 1.14lbs S.D. = 0.36lbs
	40mm N=15		40mm: Mean = 1.11lbs. S.D.=0.43lbs.
Force into Pod	17mm N= 17	6 lbs max (applies to all sizes)	17mm: Mean= 1.43 lbs S.D. = 0.46lbs
	23mm N=11		23mm: Mean= 1.74lbs S.D. = 0.61lbs
	40mm N=15		40mm: Mean=2.46lbs. S.D.=0.58lbs.
Force out of Pod	17mm N= 17	8 lbs max (applies to all sizes)	17mm: Mean= 1.33lbs S.D. = 0.49lbs
	23mm N=11		23mm: Mean= 1.64lbs S.D. = 0.30lbs
	40mm N=15		40mm: Mean=2.61lbs S.D.=0.62lbs
Springback gap	17mm N= 68	After being subjected to a loading and deployment cycle, the distance between the proximal and distal sides must be ≤ 4 mm. (applies to all sizes)	17mm: Mean = 0.25mm S.D. = 0.40mm
	23mm N=44		23mm: Mean= 0.015mm S.D. = 0.098mm
	40mm N=60		40mm: Mean=0.04mm S.D.=0.28mm
Ball to Ball Strength	N=30	6 lbs min (applies to all sizes)	Mean= 9.22lbs S.D. = 0.68lbs

9.3 Sterility and Shelf Life Qualification Studies

The method of sterilization for both the CardioSEAL and delivery system is 100% ETO. The product may be sterilized no more than twice and is validated to achieve a SAL of 10^{-6} using method C of the International Document #ISO 11135, 1994 (adopted by the Committee for the Advancement of Medical Instrumentation.).

To support a 4 year shelf life, the sterility and integrity of CardioSEAL and delivery catheters, aged out to 4 years (real-time plus accelerated aged) was tested. This involved testing both the packaging and the device.

Shipping tests in accordance with the ASTM D4169, ISTA 1A tested the packaging of the CardioSEAL and delivery catheters. All packages were found intact without evidence of physical damage. Fifteen packages each of CardioSEAL devices and delivery catheters were burst tested and found to be within the test specification.

Sterility testing was conducted on 6 samples each of the CardioSEAL and delivery catheter. All samples were found to be sterile. Bond strength and functionality testing were conducted on 5 to 20 samples real time and accelerated aged out to 4 years and exposed to shipping stresses. All test results indicate that the product performs within specification and that sterility is maintained over a period of four years.

9.4 Animal Testing

Following successful initial acute studies, three chronic animal studies were conducted to evaluate the CardioSEAL using both sheep and dog models. Explants occurred at the following timepoints: 2 weeks, 30 days, 90 days, 6 months, 1 year, and 2 years. Atrial septal defects were created either via blade septostomy or Brockenbrough followed by balloon dilation. In the first study, oversized devices were placed in freshly created defects, which resulted in thrombosis and a device arm fracture. It was later confirmed that devices implanted in freshly created defects had higher levels of protein deposition and thrombosis.

The next two studies were conducted in both the sheep and dog model with defects created a minimum of 2 weeks prior to device implantation. These both resulted in an acceptable histological response. One arm fracture occurred at 30 days in a device, which did not appear to be appropriately placed within the ASD. Friction lesions were noted acutely near the suture coil location of arms not yet healed to the septal wall surface; these healed over time. The 3 month, 6 month, 1 year, and 2 year explants showed good fibrous tissue overgrowth and endothelialization with no recent thrombosis or arm fractures.

10. CLINICAL STUDIES:

Study Design/Objective: The multi-center clinical trial conducted by Children's Hospital, Boston, Massachusetts, is a prospective, non-randomized trial studying the use of the CardioSEAL® Septal Occlusion system to close a variety of hemodynamically significant cardiac defects (e.g., fenestrated fontans, ventricular septal defects, atrial septal defects). The risks of surgical closure for the patients enrolled in this trial are sufficient to justify the known and potentially unknown risks of transcatheter closure with the CardioSEAL device. The study (referred to as the High-risk study) is ongoing and is summarized below. Data from patients undergoing PFO closure, who had failed conventional drug therapy as evidenced by a recurrent stroke, was extracted from this study as well as patients who were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy ; a medical or occupational contraindication to anticoagulation; could not tolerate anticoagulation ; and presence of a thrombus in the right atrium.

Patient Entry: Patients were eligible for enrollment in the High risk study if they had a defect(s) of sufficient size to require closure, but were considered to be at high risk for surgical closure, due to either complex medical or cardiac disease. An independent peer review group determined whether a patient should be enrolled into the trial based on the following criteria:

- the patient had a type of defect that was technically difficult or impossible to close surgically, such that the surgical risks were sufficient to justify the known and potential unknown risks of the device, or
- the patient's overall medical condition was such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

Methods: After enrollment, patients underwent cardiac catheterization. Position and size of the defect were confirmed by angiography. A hemodynamic assessment was performed pre-implant, and after test occlusion of the defect with a balloon. When these data suggested that the defect contributed to unfavorable hemodynamics and was feasible for transcatheter closure, device placement proceeded. Patients received aspirin, 1mg/kg/day, rounded to the nearest half tablet of 80 mg size, for at least six months following the procedure.

Patients were seen for follow up assessments as described in Table 4:

Timing of Evaluations - Table 4						
	Pre-Implant	Pre-D/C	1 month F/U	6 month F/U	12 month F/U	24 month F/U
Cardiac HX/PE	X	X	X	X	X	X
Chest X-Ray	X	X	X	X	X	
Fluoroscopy				X		X
Echo/Doppler	X	X	X	X	X	X
Clinical Status Evaluation	X	X	X	X	X	X
EKG (rhythm)	X	X	X	X	X	X

Primary Endpoints:
Clinical Status Scale

A 6-category ordinal scale was used to measure clinical status. The scale takes values from 0 to 5, and was constructed so that an improvement by one category would be clinically relevant.

The Clinical status scale consists of seven different classes representing important aspects of overall cardiac and medical status: right to left shunt, left to right shunt, risk for systemic emboli, hemodynamic compromise not due to shunt, arrhythmia, elevated pulmonary vascular resistance, and medical illness. The condition most closely related to a patient's indication for device closure is identified, and the patient is placed in the lowest possible category according to criteria for that class.

All of the patients undergoing device placement for PFO closure to prevent neurological injury are evaluated using the criteria in Table 5 for patients with systemic emboli. A trivial or no residual leak status was considered the same as having no intracardiac potential for emboli. Embolic events, presumed or confirmed to be due to emboli include, both transient or permanent events resulting in symptoms.

Clinical Status Scale ¹ - Table 5						
Category	0	1	2	3	4	5
Systemic embolic	NA	Recurrent embolic events, on Coumadin	Recurrent embolic events, but no anticoagulation	Single embolic events	Potential for embolic event	No intra-cardiac potential for emboli

¹A deceased patient is rated as -1 on the Clinical Status Scale.

Additionally an assessment of the echocardiographic closure status was made at each time point both at the evaluating facility, and by an unaffiliated core laboratory. Residual flow was assessed using Doppler color flow mapping, and graded using the following guidelines:

"Trivial" to "Absent": barely detectable or no detectable residual color flow through the defect. If flow is present, it is a single color flow jet, well-circumscribed, with a proximal jet width measuring less than 1 mm in diameter in all views.

"Small": single color flow jet, well-circumscribed, and measuring 1-2mm (maximal proximal width) in all views in infants and children weighing less than 20 kg, or between 1 and 3 mm in diameter in larger children and adults.

"More than small": single color flow jet, well-circumscribed, measuring greater than 2 mm in diameter in all views in infants and children weighing less than 20 kg, or greater than 3 mm in diameter in all views in larger children and adults.

Results: At the time the PFO data was analyzed, 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke and 29 patients who were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy (9); a medical or occupational contraindication to anticoagulation (17); could not tolerate anticoagulation (2); and presence of a thrombus in the right atrium (1) were enrolled in the study for PFO closure. Enrollment occurred at four investigational sites.

Among the 6 patients treated with a CardioSEAL device who had failed conventional drug therapy as evidenced by a recurrent stroke, there were 3(50%) males and 3 (50%) females. The age of the patients ranged from 35.4 years to 60.7 years, with a median age of 48.8 years.

Among the 29 patients treated with a CardioSEAL device who were at risk of a neurologic injury, there were 14(48.3%) males and 15 (51.7%) females. The age of the patients ranged from 5.3 years to 73.2 years, with a median age of 34.7 years.

Device placement was successful in all 35 patients in whom an implant was attempted. A single device was implanted in each patient. Device sizes included: (6) 23mm, (9) 28mm, (18) 33mm and (2) 40mm device. All of the implanted devices remained stable throughout the follow-up period. None of the devices embolized or were explanted.

Table 6A reflects the number of patients observed within each clinical status category at each visit for the 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke.

Clinical Status by Lesion – Table 6A										
	Category									
Timepoint	-1	0	1	2	3	4	5	Uncertain	Missing	Not Due
Initial	0	0	6	0	0	0	0	0	0	0
Discharge	0	0	0	0	0	2	3	1	0	0
1 Month	0	0	0	0	0	1	4	0	1	0
6 Month	0	0	0	0	0	0	2	1	3	0
12 Month	0	0	0	0	0	1	4	1	0	0
24 Month	0	0	0	0	0	0	0	0	1	5

Table 6B reflects the number of patients observed within each clinical status category at each visit for the 29 patients who were at risk of a neurologic injury.

Clinical Status by Lesion Table 6B										
	Category									
Timepoint	-1	0	1	2	3	4	5	Uncertain	Missing	Not Due
Initial	0	0	9	3	16	1	0	0	0	0
Discharge	0	0	1	0	1	8	16	3	0	0
1 Month	0	0	0	1	0	5	17	3	3	0
6 Month	0	0	0	0	0	4	16	3	0	6
12 Month	1	0	0	0	0	1	7	4	1	15
24 Month	0	0	0	0	0	0	5	0	2	22

Table 7A reflects the number of patients observed within each Echo Closure category at each visit for the 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke.

Echo Closure Status – Table 7A						
	Category					
	None-Trivial	Small	Greater than small	Uncertain	Missing	Not due
Initial	0	2	0	4	0	0
Discharge	1	1	0	4	0	0
1 Month	1	1	0	2	2	0
6 Month	3	0	0	1	2	0
12 Month	4	1	0	0	1	0
24 Month	0	0	0	0	1	5

Table 7B reflects the number of patients observed within each Echo Closure category at each visit for the 29 patients who were at risk of a neurologic injury.

Echo Closure Status – Table 7B						
	Category					
	None-Trivial	Small	Greater than small	Uncertain	Missing	Not due
Initial	7	13	2	7	0	0
Discharge	21	5	0	3	0	0
1 Month	17	1	0	4	7	0
6 Month	19	1	0	2	1	6
12 Month	8	0	0	4	2	15
24 Month	5	0	0	0	2	22

11. Conclusions Drawn from the Studies

The pre-clinical studies indicate that the CardioSEAL Septal Occlusion System is biocompatible and has the appropriate physical and performance characteristics for its intended use, as stated in the labeling.

The clinical data generated from the High-risk study at Children's Hospital, Boston, Massachusetts indicates patients will not be exposed to an unreasonable or significant risk of illness or injury, and that the probable benefit to health from the use of the device outweighs the risk of injury or illness, taking into account the probable risks and benefits of alternative forms of treatment.

The preclinical studies and the clinical data from the High-risk study provide reasonable assurance of the safety and probable benefit of the CardioSEAL Septal Occlusion System when used in accordance with its labeling.

12. Panel Recommendations

A Circulatory System Devices Panel advisory meeting was not held to discuss this device. However, a general Panel meeting was held on October 24, 1997, where a lengthy discussion of clinical requirements for this category of devices, i.e., occlusion devices intended to treat congenital heart disease, took place. Based on a review of these recommendations and the data in the HDE, it was determined that a Panel meeting was not necessary for this device.

12. FDA Decision

CDRH determined that, based on the data submitted in the HDE, the CardioSEAL Septal Occlusion System will not expose patients to an unreasonable risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval on _____.

13. Approval Specifications

Indications for Use: See the Instructions for Use (Attachment 1)

Hazards to Health from Use of the Device: See CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, and ADVERSE EVENTS in the Instructions for Use (Attachment 1)

LABELING



The CardioSEAL® Septal Occlusion System
Instructions for Use for PFO closure
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INSTRUCTIONS FOR USE

The CardioSEAL Septal Occlusion System

Federal law (USA) restricts this device to sale by or on the order of a physician (or properly licensed practitioner).

1. HUMANITARIAN USE DEVICE: Authorized by Federal law for use in the treatment of patients with a patent foramen ovale (PFO) with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.

The effectiveness of this device for use in this indication has not been demonstrated.

2. PRODUCT DESCRIPTION:

The CardioSEAL Septal Occlusion System consists of two primary components:

- The CardioSEAL (Occluder), which is constructed of a metal (MP35n) framework to which polyester fabric is attached, and
- The Delivery Catheter, a coaxial polyurethane catheter designed specifically to facilitate attachment, loading, delivery and deployment of the CardioSEAL to the defect.

3. INDICATION FOR USE:

The CardioSEAL Septal Occlusion System is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

The CardioSEAL Septal Occlusion System is indicated for the closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.

Cryptogenic stroke is defined as a stroke occurring in the absence of potential phanerogenic cardiac, pulmonary, vascular or neurological sources. Conventional drug therapy is defined as a therapeutic INR on oral anticoagulants.

The effectiveness of this device in this indication has not been demonstrated.

4. CONTRAINDICATIONS:

Presence of thrombus at the intended site of implant, or documented evidence of venous thrombus in the vessels through which access to the defect is gained.

Active endocarditis, or other infections producing a bacteremia.

Patients whose vasculature, through which access to the defect is gained, is inadequate to accommodate the appropriate size sheath.

Patients whose defect is too small to allow the 11 F sheath to cross the defect.

Anatomy in which the CardioSEAL size required would interfere with other intracardiac or intravascular structures, such as valves or pulmonary veins.

Patients with coagulation disorders who are unable to take antiplatelet or, anticoagulant therapy.

Patients with known hypercoagulable states.

Patients with an intra-cardiac mass or vegetation.

5. WARNINGS:

This device should only be used by those physicians trained in transcatheter defect closure techniques, and by those physicians prepared to provide long term follow up patient monitoring.

Physicians attempting to recover an embolized device should be limited to those that have completed appropriate device retrieval technique training.

Embolized CardioSEAL devices should be removed. Dislodged CardioSEALs have embolized to the pulmonary and systemic vasculature.

Embolized CardioSEALs may disrupt critical cardiac functions. Physicians must be prepared to deal with urgent requirements to extract or move embolized CardioSEALs that result in critical hemodynamic compromise.

Embolized CardioSEALs should not be withdrawn through intracardiac structures unless they have been adequately collapsed within a sheath. Devices that are not adequately collapsed within a sheath may entangle with valvular or other cardiac structures.

Do not attempt to repair or reuse damaged product. Do not reuse or resterilize product. Return to manufacturer.

Surgical support should be readily available if needed.

Transient hemodynamic compromise may be encountered during device placement, which may require fluid replacement or other medications as determined by the physician.

6. PRECAUTIONS:

6.1 CardioSEAL – Handling Precautions

Do not use the system if, during loading of the CardioSEAL, difficulty is encountered in transferring the CardioSEAL into the loader or from loader to the pod of the delivery catheter.

Do not modify the delivery catheter or CardioSEAL. Modification may result in damage that can result in complications such as embolism, framework fracture, failure to release, and improper seating at the target defect.

6.2 CardioSEAL – Sizing Precautions

The use of a compliant balloon catheter to determine defect localization is recommended.

Accurate defect sizing is critical to CardioSEAL selection. Defect sizing methods, such as contrast angiography, echocardiography and – or balloon sizing should be considered as procedural alternatives.

The anatomic area surrounding the target defect should have enough contiguous structure to support the CardioSEAL.

The defect and surrounding structures should be fully examined in multiple planes to assure proper sizing of the CardioSEAL and to detect any unusual anatomy.

6.3 CardioSEAL – Procedural Precautions

The ability of the patient to remain still during implantation must be weighed against the need for "conscious" sedation versus general anesthesia. The decision to use general anesthesia in any individual patient is subject to physician judgement.

Patients should be fully heparinized throughout the procedure using adequate dosing so as to keep the ACT greater than 200 msec.

Antibiotic therapy perioperatively is recommended to reduce the risk of perioperative infection.

The use of Transesophageal Echocardiography (TEE) should be considered as a potential aid in placing the CardioSEAL. If used, the patient's esophageal anatomy must be adequate for placement and manipulation of the TEE probe.

Placement of the CardioSEAL requires the use of fluoroscopic X-ray guidance. The risk of increased x-ray exposure for patients who are pregnant must be weighed against the potential benefits of the technique.

The patient's vasculature should be sufficient to accommodate the 11 F sheath required to deliver the CardioSEAL.

Introducer sheaths longer than 80 cm will prohibit the complete extrusion of the CardioSEAL from the sheath during delivery to the defect.

A delivery catheter of equivalent or larger pod size must be used with the CardioSEAL to avoid damage to the implant during loading and deployment.

Care should be taken not to entrap right atrial Chiari networks or large Eustachian valves under the right atrial side of the device.

Malpositioned CardioSEALs may interfere with cardiac, vascular or valvular structures, depending on patient anatomy. Physicians should consider removing malpositioned CardioSEALs in these patients.

6.4 CardioSEAL – Post Implant Precautions

The time course of endothelialization of the device is unknown. Patients should receive appropriate endocarditis prophylaxis for the six months following implantation. The decision to continue prophylactic treatment after six months is subject to physician judgement.

Patients should be treated with antiplatelet/anticoagulation therapy, (see Section 8 Clinical Studies for the dosage used in the High-risk study) for six-months following implant. The decision to continue medical treatment beyond six months is subject to physician judgement.

If a left sided thrombus is identified, the patient should be evaluated for a hypercoagulable state and initiation of aggressive anticoagulant therapy should be given. Thrombolysis and surgical removal should be considered if the patient does not respond to the anticoagulant therapy.

All CardioSEALs are non-ferromagnetic. Independent studies of CardioSEAL in a 1.5 Tesla magnetic field demonstrate no movement of the CardioSEAL. However, MRI image quality may be compromised in the area of the implant.

7. ADVERSE EVENTS:

7.1 Observed Adverse Events:

In a 292 patient multi-center High Risk study, 35 patients underwent closure of a PFO to prevent neurological injury. Six (6) patients had failed conventional drug therapy as evidenced by a recurrent stroke and 29 were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy (9); a medical or occupational contraindication to anticoagulation (17); could not tolerate anticoagulation (2); and presence of a thrombus in the right atrium (1).

One patient died of lung cancer while in the study. Eighteen (18) patients have completed a 12 month follow-up visit and five patients completed a 24 month visit.

A total of 44 adverse events were recorded among the 35 patients enrolled in the study for closure of their PFO. These adverse events were classified as Serious (4), Moderately Serious (16), Not Serious (23), or Unknown Seriousness (1) and were linked to either the device, the implant procedure, the catheterization procedure, or other causes, such as a pre-existing condition. Of these 44 adverse events, 7 events were definitely, probably or possibly related to the device, the implant procedure, or the catheterization. All 7 of these events were classified as moderately serious (Table 1).

Adverse Events – Table 1 PFO (n=35)		
	Moderately Serious	
	Early Event*	Late Event**
Device Related		
Transient Neurological symptoms	2	0
Implant Procedure Related		
None	0	0
Catheterization Procedure Related		
ST elevation	1	0
Brachial plexus injury	1	0
Rash	1	0
Pseudoaneurysm at vascular access site	1	0
Tachycardia	1	0

* = Early event is \leq 30 days from implant. Total =1 early event.

** = Late event is > 30 days from implant. Total =0 late events.

In this study, fractures of the framework have been reported in 9 out of 35 implanted patients. The risk of fracture appears to be related to the size of the Occluder selected relative to the size of the heart chamber. There have been two reports of palpitations which were considered possibly related to device arm fracture. In both cases, they were classified as not serious.

7.2 Potential Adverse Events:

Placement of the CardioSEAL involves using standard interventional cardiac catheterization techniques. Complications commonly associated with these procedures include, but are not limited to:

- Air Embolus
- Allergic dye reaction
- Anesthesia reactions

- Apnea
- Arrhythmia
- Death
- Fever
- Headache / Migraines
- Hematoma and/or Pseudoaneurysm including blood loss requiring transfusion
- Hypertension; Hypotension
- Infection including Endocarditis
- Perforation of Vessel or Myocardium
- Stroke / Transient Ischemic Attack
- Thromboembolic events
- Valvular regurgitation.

7.3 Observed Device Malfunctions:

There were no reports of device malfunctions in this PFO population. However, there were 4 device malfunctions in a supporting cohort of patients with atrial level defects. These malfunctions included: one report of a kink in the delivery system, identified during the device placement; one report of a difficult release, the device was subsequently not used; one report of a device which did not open the device was subsequently not used; and one report of difficulty advancing the device through the pod resulting from the physician modifying the delivery system. There were no clinical sequelae associated with any of these device malfunctions.

8. CLINICAL STUDIES:

Study Design/Objective: The multi-center clinical trial conducted by Children's Hospital, Boston, Massachusetts, is a prospective, non-randomized trial studying the use of the CardioSEAL® Septal Occlusion system to close a variety of hemodynamically significant cardiac defects (e.g., fenestrated forams, ventricular septal defects, atrial septal defects). The risks of surgical closure for the patients enrolled in this trial are sufficient to justify the known and potentially unknown risks of transcatheter closure with the CardioSEAL device. The study (referred to as the High-risk study) is ongoing and is summarized below. Data from patients undergoing PFO closure, who had failed conventional drug therapy as evidenced by a recurrent stroke, was extracted from this study as well as patients who were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy ; a medical or

occupational contraindication to anticoagulation; could not tolerate anticoagulation ; and presence of a thrombus in the right atrium.

Patient Entry: Patients were eligible for enrollment in the High risk study if they had a defect(s) of sufficient size to require closure, but were considered to be at high risk for surgical closure, due to either complex medical or cardiac disease. An independent peer review group determined whether a patient should be enrolled into the trial based on the following criteria:

- the patient had a type of defect that was technically difficult or impossible to close surgically, such that the surgical risks were sufficient to justify the known and potential unknown risks of the device, or
- the patient's overall medical condition was such that the surgical risks were sufficient to justify the known and potential unknown risks of the device.

Methods: After enrollment, patients underwent cardiac catheterization. Position and size of the defect were confirmed by angiography. A hemodynamic assessment was performed pre-implant, and after test occlusion of the defect with a balloon. When these data suggested that the defect contributed to unfavorable hemodynamics and was feasible for transcatheter closure, device placement proceeded. Patients received aspirin, 1mg/kg/day, rounded to the nearest half tablet of 80 mg size, for at least six months following the procedure.

Patients were seen for follow up assessments as described in Table 2:

	Pre-Implant	Pre-D/C	1 month F/U	6 month F/U	12 month F/U	24 month F/U
Cardiac HX/PE	X	X	X	X	X	X
Chest X-Ray	X	X	X	X	X	
Fluoroscopy				X		X
Echo/Doppler	X	X	X	X	X	X
EKG (rhythm)	X	X	X	X	X	X
Clinical Status	X	X	X	X	X	X

Primary Endpoints: A 6-category ordinal scale was used to measure clinical status. The scale takes values from 0 to 5, and was constructed so that an improvement by one category would be clinically relevant.

The Clinical status scale consists of seven different classes representing important aspects of overall cardiac and medical status: right to left shunt, left to right shunt, risk for systemic emboli, hemodynamic compromise not due to shunt, arrhythmia, elevated pulmonary vascular resistance, and medical illness. The condition most closely related to a patient's indication for device closure is identified, and the patient is placed in the lowest possible category according to criteria for that class.

All of the patients undergoing device placement for PFO closure to prevent neurological injury are evaluated using the criteria in Table 3 for patients with systemic emboli. A trivial or no residual leak status was considered the same as having no intracardiac potential for emboli. Embolic events, presumed or confirmed to be due to emboli include, both transient or permanent events resulting in symptoms.

Table 3 Clinical Status Scale

Category	0	1	2	3	4	5
Systemic embolic	N/A	recurrent embolic events, on Coumadin	Recurrent embolic events, but no anticoagulant	single embolic event	potential for embolic event	no intra-cardiac potential for emboli

Note: a deceased patient is rated as -1 on the Clinical Status Scale.

Additionally an assessment of the echocardiographic closure status was made at each time point both at the evaluating facility, and by an unaffiliated core laboratory. Residual flow was assessed using Doppler color flow mapping, and graded using the following guidelines:

"Trivial" to "Absent": barely detectable or no detectable residual color flow through the defect. If flow is present, it is a single color flow jet, well-circumscribed, with a proximal jet width measuring less than 1 mm in diameter in all views.

"Small": single color flow jet, well-circumscribed, and measuring 1-2mm (maximal proximal width) in all views in infants and children weighing less than 20 kg, or between 1 and 3 mm in diameter in larger children and adults.

"More than small": single color flow jet, well-circumscribed, measuring greater than 2 mm in diameter in all views in infants and children weighing less than 20 kg, or greater than 3 mm in diameter in all views in larger children and adults.

Results: At the time the PFO data was analyzed, 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke and 29 patients who were at risk of a neurologic injury for the following reasons: recurrent embolic events despite medical therapy (9); a medical or occupational contraindication to anticoagulation (17); could not tolerate anticoagulation (2); and presence of a thrombus in the right atrium (1) were enrolled in the study for PFO closure. Enrollment occurred at four investigational sites.

Among the 6 patients treated with a CardioSEAL device who had failed conventional drug therapy as evidenced by a recurrent stroke, there were 3(50%) males and 3 (50%) females. The age of the patients ranged from 35.4 years to 60.7 years, with a median age of 48.8 years.

Among the 29 patients treated with a CardioSEAL device who were at risk of a neurologic injury, there were 14(48.3%) males and 15 (51.7%) females. The age of the patients ranged from 5.3 years to 73.2 years; with a median age of 34.7 years.

Device placement was successful in all 35 patients in whom an implant was attempted. A single device was implanted in each patient. Device sizes included: (6) 23mm, (9) 28mm, (18) 33mm and (2) 40mm device. All of the implanted devices remained stable throughout the follow-up period. None of the devices embolized or were explanted.

Table 4A reflects the number of patients observed within each clinical status category at each visit for the 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke.

Clinical Status by Lesion - Table 4A										
Timepoint	Category									
	-1	0	1	2	3	4	5	Uncertain	Missing	Not Due
Initial	0	0	6	0	0	0	0	0	0	0
Discharge	0	0	0	0	0	2	3	1	0	0
1 Month	0	0	0	0	0	1	4	0	1	0
6 Month	0	0	0	0	0	0	2	1	3	0
12 Month	0	0	0	0	0	1	4	1	0	0
24 Month	0	0	0	0	0	0	0	0	1	5

Table 4B reflects the number of patients observed within each clinical status category at each visit for the 29 patients who were at risk of a neurologic injury.

Clinical Status by Lesion Table 4B										
Timepoint	Category									
	-1	0	1	2	3	4	5	Uncertain	Missing	Not Due
Initial	0	0	9	3	16	1	0	0	0	0
Discharge	0	0	1	0	1	8	16	3	0	0
1 Month	0	0	0	1	0	5	17	3	3	0
6 Month	0	0	0	0	0	4	16	3	0	6
12 Month	1	0	0	0	0	1	7	4	1	15
24 Month	0	0	0	0	0	0	5	0	2	22

Table 5A reflects the number of patients observed within each Echo Closure category at each visit for the 6 patients who had failed conventional drug therapy as evidenced by a recurrent stroke.

Echo Closure Status - Table 5A						
	Category					
	None-Trivial	Small	Greater than small	Uncertain	Missing	Not due
Initial	0	2	0	4	0	0
Discharge	1	1	0	4	0	0
1 Month	1	1	0	2	2	0
6 Month	3	0	0	1	2	0
12 Month	4	1	0	0	1	0
24 Month	0	0	0	0	1	5

Table 5B reflects the number of patients observed within each Echo Closure category at each visit for the 29 patients who were at risk of a neurologic injury.

Echo Closure Status - Table 5B						
	Category					
	None-Trivial	Small	Greater than small	Uncertain	Missing	Not due
Initial	7	13	2	7	0	0
Discharge	21	5	0	3	0	0
1 Month	17	1	0	4	7	0
6 Month	19	1	0	2	1	6
12 Month	8	0	0	4	2	15
24 Month	5	0	0	0	2	22

9. HOW SUPPLIED:

The implant and delivery system are packaged separately. The delivery system is size matched to the implant. Both components are provided sterile. Product is sterilized via ETO.

10. DIRECTIONS FOR USE:

A. Detailed Product Description:

The CardioSEAL Septal Occlusion System consists of two primary components. The CardioSEAL (Occluder) is comprised of a metal alloy (MP35n) framework to which polyester fabric material has been attached.

From the center of the CardioSEAL, a small wire with a pin at its end extrudes out at approximately 90 degrees to the plane of the CardioSEAL. The CardioSEAL is attached to sutures through a loading funnel. The loader should always be connected via sutures to the side of the CardioSEAL opposite the side from which the pin wire extrudes.

The delivery catheter is comprised of a coaxial catheter shaft through which a spring guide travels, connected to a solid control rod. At the proximal end of the control rod, a control handle is connected to an inner control wire, which courses through the spring guide to the distal end of the catheter shaft, where it terminates within a small tubular sleeve. The control wire terminates at the distal end in a pin, for attachment to its mate on the CardioSEAL. When retracted, the pin slides inside the sleeve. The distal end of the catheter terminates in a pod. Retraction on the control rod moves the sleeve into the pod. Refer to figure 1 for an illustration of the delivery system and CardioSEAL.

B. CardioSEAL Size Selection and Inspection:

Selection of an appropriately sized CardioSEAL(O) should be based upon measuring the defect diameter through the use of a sizing balloon (stretched defect diameter - SDD), procedural angiography and/or transesophageal echocardiography, unless the size of the defect is known from the medical record. It is recommended that the CardioSEAL to Stretched Defect Diameter ratio (O:SDD) be 1.7-2.0:1, and that the area containing the target defect be large enough to allow the CardioSEAL to fully deploy. The defect and surrounding structures should be fully examined in multiple planes to assure proper sizing of the CardioSEAL.

The Right Femoral Vein is recommended for vascular access although physicians should consider defect location and the route of introducer sheath travel relative to the potential for access in selecting the venous access site.

An 11F, 75cm long, hemostasis control introducer sheath with NIH type curve is recommended for CardioSEAL delivery. Sheath curve shape may need modification

based on individual patient conditions and defect location. As the use of long sheaths represents a potential risk of air embolus, care should be taken to insure adequate irrigation and 'backfilling' of the sheath with saline during removal of the dilator in order to avoid air entry.

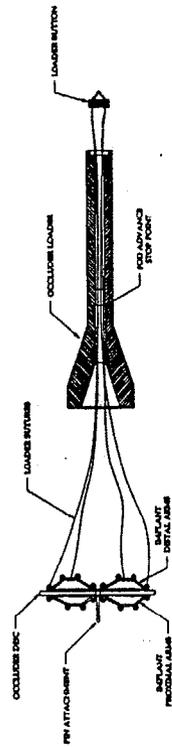
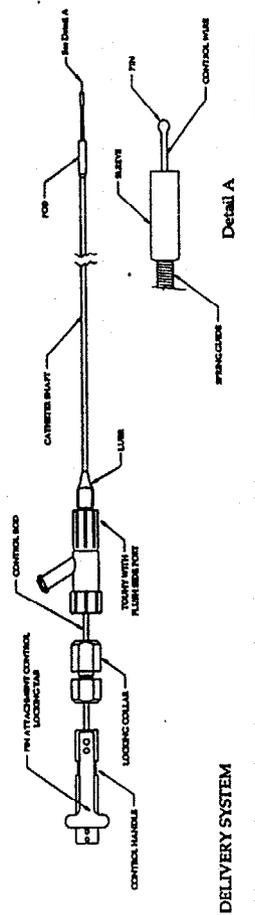
A 14F or 16F short introducer sheath may be placed coaxially over the long introducer sheath prior to long sheath insertion if the physician believes the circumstances of the case raise the potential for device retrieval after attempted placement.

Prior to use, inspect the delivery system and CardioSEAL for signs of damage, such as kinks or bends in delivery wire or framework of the CardioSEAL. Check for secure attachment of the fabric to the framework.

Manipulate the delivery system and actuate the control handle to ensure that the attach release pin exits and retracts into the sleeve, and that the spring guide wire exits and retracts into the pod.

The delivery catheter system and CardioSEAL are packaged separately. Each is a component of the system, however, and each implant requires an equivalently sized or larger delivery catheter for appropriate use.

The CardioSEAL™ Septal Occlusion System



OCCLUDER

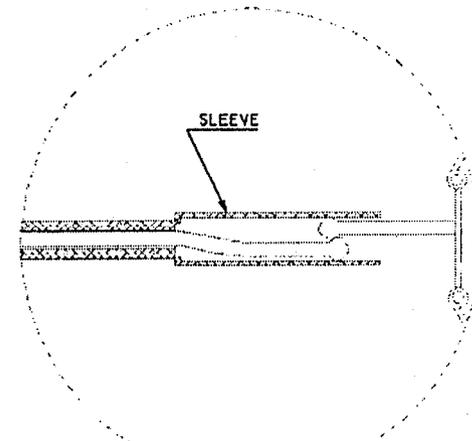
FIGURE #1

C. Preparation for Delivery:

Attaching the CardioSEAL to the Delivery Catheter:

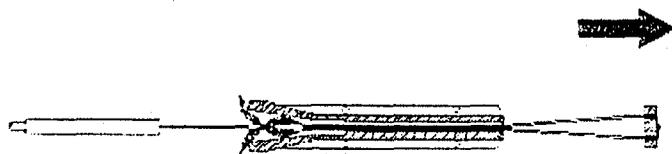
NOTE: Attachment and loading of the CardioSEAL into the delivery catheter should not occur until

- the defect has been determined to be of appropriate size and position to accommodate the CardioSEAL, and
 - access to the defect with an appropriate French size and length introducer sheath has been obtained.
- Loosen the black locking collar on the delivery catheter and advance the control rod until the sleeve exits from the pod. Pull gently upward on the pin control locking tab on the control handle. Push the rear section of the control handle in, extruding the pin from the sleeve about 3 – 4 mm.
 - Place the pin of the CardioSEAL into the sleeve, behind the pin extruding from the sleeve. Draw both pins into the sleeve by lifting up on the control handle tab and pulling the rear section of the control handle out. Seat control tab into slot on control handle, and test for secure attachment of CardioSEAL to delivery system with a gentle to and fro motion of the CardioSEAL.



- Submerge the loader/ CardioSEAL assembly in sterile saline and thoroughly soak the CardioSEAL. Make sure inner lumens of loader are wet. This will decrease friction between CardioSEAL and loader during loading.

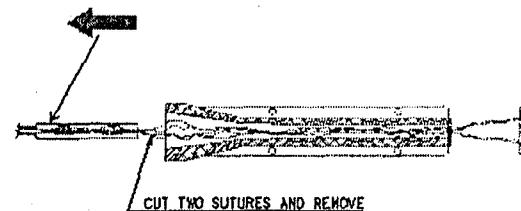
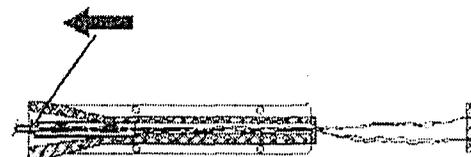
4. Carefully draw the CardioSEAL into the smallest section of the loader by pulling on the loader button. Do not attempt to force CardioSEAL into funnel section of the loader unless all four arms on each side of the CardioSEAL are appropriately retracted into the collapsed position.



5. With the CardioSEAL fully collapsed in the smallest section of the loader, use the control rod to advance the pod into the loader until the pod contacts the stop point.



6. Holding the pod firmly in the loader, retract CardioSEAL into the pod through the use of the control rod. Once in the pod, remove pod from loader, snip sutures one at a time, and remove from the CardioSEAL. Discard loader, sutures and loader button.

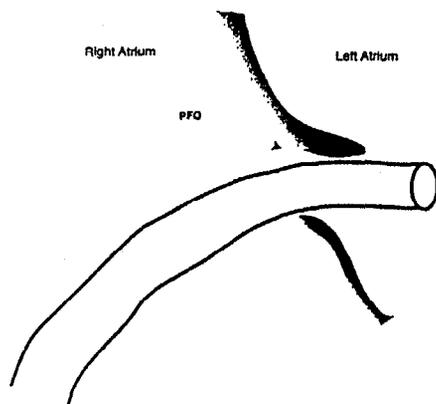


7. Loosen locking collar and advance it up to the Y-body. Tighten locking collar and flush the delivery system with normal saline several times to remove all air from the system. The CardioSEAL is now ready for delivery to the defect.

D. Insertion

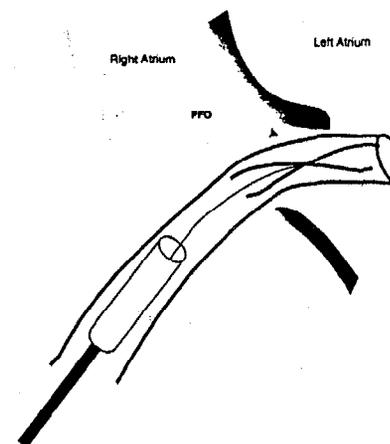
NOTE: As previously discussed in Section C, Preparation, Note B, an introducer sheath of sufficient French size (11F) for the CardioSEAL and of adequate length to reach the target defect should have been placed via the venous system across the defect.

1. Reposition sheath across the defect so that the distal tip of the sheath is approximately 1cm into the distal side of the defect. Thoroughly irrigate the previously placed introducer sheath to minimize risk of air entry and air embolus.

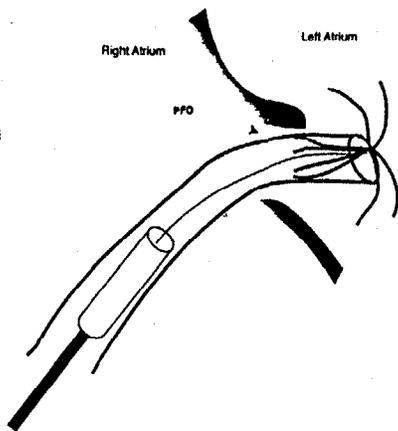


2. Insert the pod of the delivery system into the sheath, and advance until the pod is no closer than 5 to 10 cm from the tip of the sheath. The pod should be in the fluoroscopic field of view.

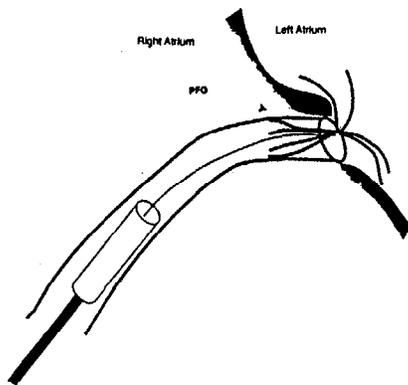
3. Loosen the locking collar nut and advance the collapsed CardioSEAL out of the pod and into the sheath. The CardioSEAL will remain collapsed within the sheath, with the sheath serving as an extension of the pod. Continue to advance the CardioSEAL until it is within 1-2mm of the tip of the sheath.



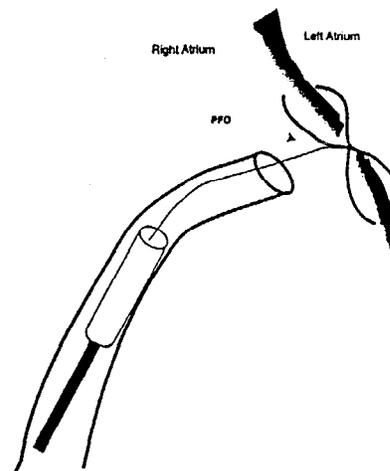
4. Recheck sheath tip position to verify location on distal side of defect. Holding the sheath and catheter steady, advance the distal set of CardioSEAL arms out of the sheath by moving the control rod forward. Alternatively, open distal set of CardioSEAL arms by retracting sheath off of the distal arms. Under fluoroscopy and Transesophageal echo, ascertain that all four distal CardioSEAL arms have fully deployed and are intact.



5. Holding the sheath and catheter steady, retract entire sheath - CardioSEAL system until the distal CardioSEAL arms approximate or engage the distal wall of the defect.

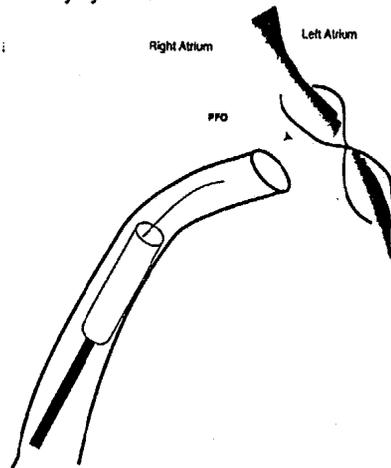


6. Once approximated or engaged, retract CardioSEAL further to slightly flex the CardioSEAL arms. Retract sheath off of proximal CardioSEAL arms while maintaining position in the defect. This will release the proximal arms of the CardioSEAL to engage the proximal defect wall.



7. Allow delivery catheter and sheath to assume a neutral (i.e. no retraction) position and confirm correct placement of all arms on appropriate sides of the defect.

8. Once proper positioning is confirmed, advance the pin from the sleeve using the control handle at the proximal end of the delivery system. This will release the CardioSEAL from the delivery system.



9. Remove delivery system from sheath.

11. PATIENT INFORMATION:

The following counseling information should be provided to the patient:

Patients should be reminded of the importance of adhering to their aspirin and endocarditis prophylaxis regimens.

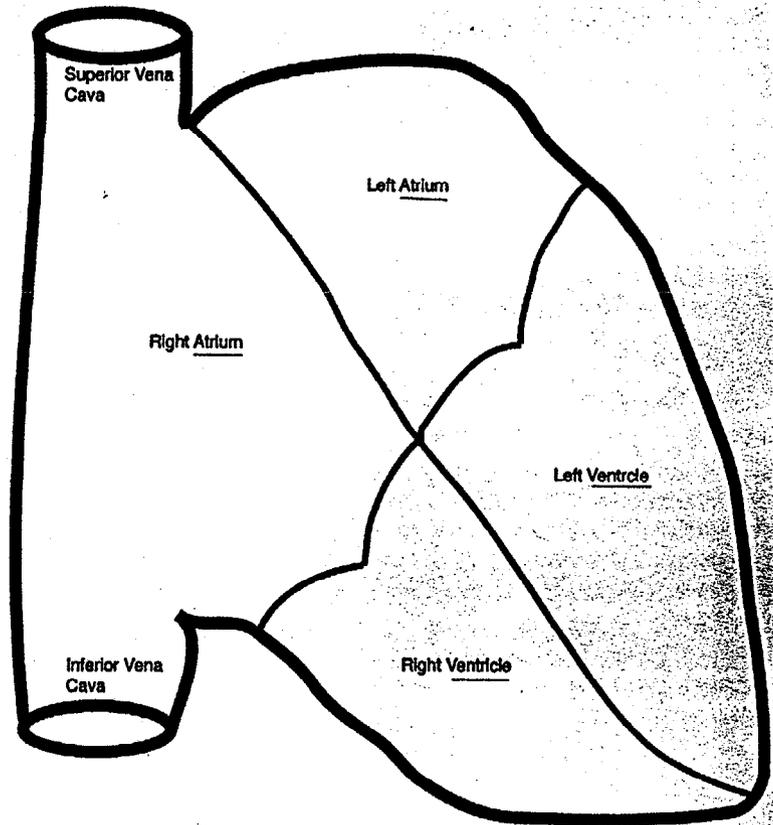
If an MRI is required, the patient should inform MRI staff of the presence of the CardioSEAL.

Patients should be encouraged to contact their physician if they have any questions or concerns

A patient brochure is available and is entitled: "A Patient's Guide to Transcatheter Defect Closure using the CardioSEAL® Septal Occlusion System."

PL#:0256.00

A Patient's Guide to Transcatheter Hole Closure of a Patent Foramen Ovale using The CardioSEAL® Septal Occlusion System



Basic Diagram of the Normal Heart

Humanitarian Use Device

The CardioSEAL Septal Occlusion System is authorized by Federal (USA) law as a Humanitarian Use Device for use in the following indication only:

The CardioSEAL Septal Occlusion System is indicated for the closure of a patent foramen ovale (PFO) in patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy.

Cryptogenic stroke is defined as a stroke occurring in the absence of potential known cardiac, pulmonary, vascular or neurological sources. Conventional drug therapy is defined as a therapeutic dosage of oral anticoagulants.

The effectiveness of this device in this indication has not been demonstrated.

Note: underlined words are defined in the Glossary of technical term.

Introduction:

You have been diagnosed by your physician as having a small hole in your heart called a Patent Foramen Ovale (PFO) which is suspected as being the pathway for a small embolus to have traveled from the right atrium to the left atrium (see diagram below). This embolus resulted in a blockage of blood flow to an artery, resulting in a paradoxical embolic event, such as a stroke. You may have had this event multiple times despite taking blood thinners.

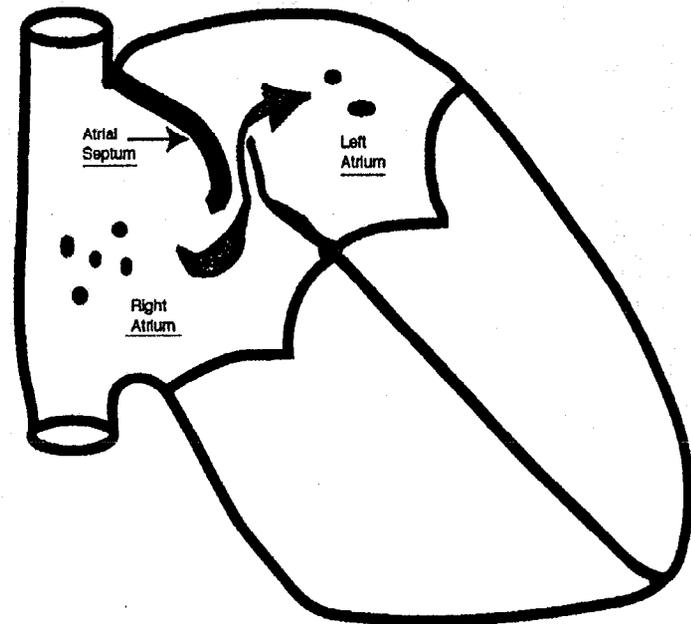


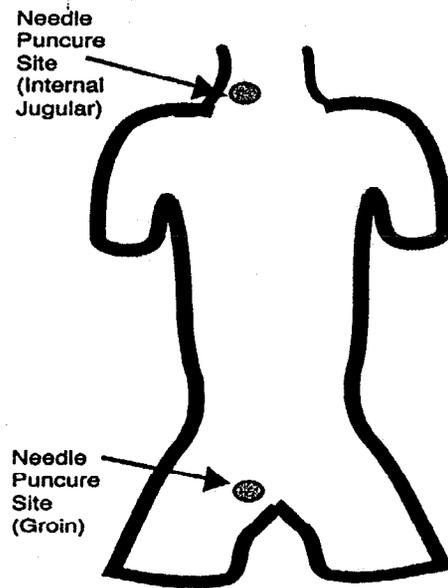
Diagram of a the Heart with a Patent Foramen Ovale (PFO)

Diagram illustrating blood flow through a Patent Foramen Ovale. The PFO is the opening through which the blood is able to flow when the pressure in the right atrium is greater than the left atrium.

Your physician has recommended that this small hole should now be closed using an implant. The implant is placed in the heart using a catheter. This procedure is called Transcatheter Hole Closure. It is an alternative to open heart surgery. The physician believes that the risks of open heart surgery to close this hole presents an unusually high risk to you. Transcatheter Hole Closure is a procedure that avoids the need for open heart surgery. As a less invasive procedure, it is believed to present fewer risks since open heart surgery is avoided.

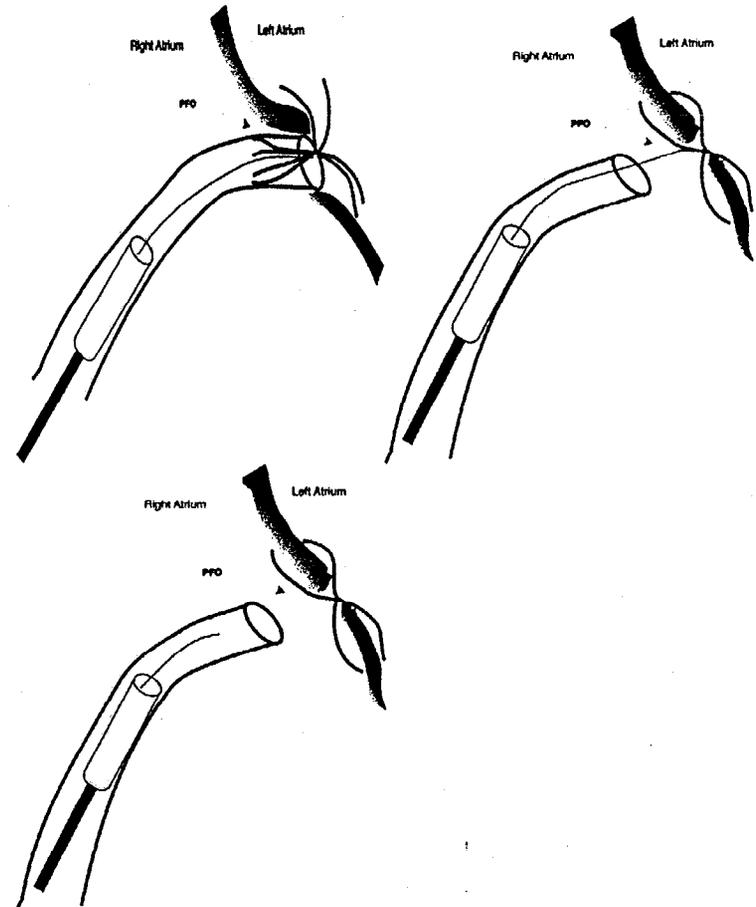
How does Transcatheter closure work?

Transcatheter Hole Closure is performed in the Cardiac Catheterization Laboratory by a Doctor. The Doctor will gain access to your (your child's) heart by getting access to a major vein in the groin or internal jugular vein.



This is done by a needle puncture. Various catheters will be advanced from the groin or neck into the heart. A test involving moving pictures of the heart, called an angiogram, will be taken to better visualize the heart and the hole. The Doctor may use a special ultrasound device, called TransEsophageal Echocardiography (TEE). This is another way to better see the heart and the hole. The TEE involves putting a probe into the esophagus, the tube between the mouth and stomach. These tests are used to determine which size implant the physician will use to close the hole.

The appropriate size implant is attached and collapsed for placement into a special catheter. The catheter is then advanced to the site of the hole. The Doctor re-expands the implant so that part of it sits on each side of the hole. In effect the hole is gently sandwiched between the two sides of the implant. The implant is then released from the catheter. The catheter is removed and the procedure completed.



Diagrams showing the basic steps of the procedure.

Will I be awake during the procedure?

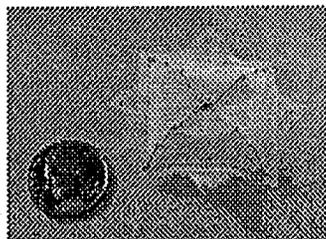
This is up to the physician. Many patients are put under general anesthesia for this procedure. A local anesthetic is used to numb the groin or neck (the location where the catheters are inserted).

How does the implant stay in place?

CardioSEAL is made from two, small diameter wire frameworks. The framework has a special fabric attached to it. The device looks like two little umbrellas set edge to edge. Each umbrella framework has special springs. This allows the umbrellas to spring towards the hole. This very slight tension, along with the blood in the heart, holds the device in place. Over time, tissue grows into the fabric and the implant becomes part of the heart.

What does the Implant look like?

CardioSEAL comes in several sizes. The smallest (17mm measured diagonally) is about the size of a dime, the largest is about size of a half-dollar. This picture shows one of the larger implants placed next to a dime. This may give you some perspective of the size. The framework is made from a metal frequently implanted in the body during other surgeries. The fabric is the same fabric the surgeon would use if open heart surgery was performed.



What are the risks?

The risks are similar to those associated with other heart catheterization procedures. There are additional risks associated with the implant. Examples include:

- dislodgement
- incomplete sealing of the hole
- abnormal heart rhythms
- bruising at the groin or arm
- changes in blood pressure
- air embolus
- hemolysis
- apnea
- headache/migraine
- infection including endocarditis
- perforation of vessel or myocardium
- thromboembolus
- stroke or TIA
- valvular regurgitation
- fracture of the implanted device
- palpitations

The implanting physician usually insures that the risks associated with heart catheterization and the implant are reviewed with each patient.

Will the procedure hurt?

Usually not. After the procedure, some patients report tenderness at the groin or arm. Some also complain of a sore throat from the TEE probe. Patients cannot “feel” the implant.

What is the special care after the procedure?

- bed rest for a period of time (this allows the implant to firmly stabilize)
- restriction from heavy lifting or other physical activities for a period of time
- take a blood thinning product, such as Aspirin, every day, for a period of time (perhaps six months or longer)
- take antibiotics to prevent infection for a period of time (perhaps six months or longer and when going to the dentist or having a minor surgical)
- follow the doctor's instructions precisely
- call the doctor if there are any questions

What about follow up visits?

All patients are asked to see their doctor for follow up visits. The Doctor will provide specific instructions for follow-up care.

Does the Implant stay in for the rest of my life?

Yes, it is intended to stay in forever.

Can I go through metal detectors, or have an M.R.I?

Yes. The implant will not set off metal detectors. The metal framework is not magnetic. It will not be affected by an MRI, but the picture taken by the MRI might have a fuzzy quality. If an MRI is needed, the MRI staff should be informed about the presence of the implant.

What are the options or alternatives to this treatment?

Having open heart surgery to close the PFO is an option. Continuing to take blood thinners is also an option. Or, you may elect to have no treatment of any kind.

What are the contraindications to this treatment?

- presence of blood clots in the vein used to introduce the catheter
- the vein needed to introduce the catheter is too small for the catheter to fit
- presence of an active infection
- patient unable to take aspirin or other blood thinning medication

Glossary of technical terms

- **Abnormal heart rhythms** – abnormal heart beats.
- **Air embolus** – an air bubble in the blood stream.
- **Angiogram** – a test involving moving pictures of the heart.
- **Apnea** – a transient cessation of breathing.
- **Atrium** – the upper two chambers (right and left) of the normal heart.
- **Cardiac Catheterization Laboratory** – a room in the hospital dedicated to accessing the heart using catheters and X-ray guidance.
- **Catheter** – a sterile tube for insertion into a vessel to permit injection or withdrawal of fluids or to pass material through.
- **Cryptogenic** – an unknown source.
- **Dislodgement** – moving from its intended position.
- **Endocarditis** – an inflammation of the lining of the heart and its valves.
- **Embolus** – an abnormal particle circulating in the blood.
- **Esophagus** – the tube between the mouth to the stomach.

- **Heart catheterization** – a less invasive way (compared to open heart surgery) to access the heart using the arteries or veins.
- **Hemolysis** – breaking of the red blood cells.
- **Implant** – a medical device which is put into the body.
- **MRI** – Magnetic Resonance Imaging--a type of test used to visualize body tissue that uses a magnetic field.
- **Palpitations** – an abnormally rapid heart beat.
- **Paradoxical Embolic Event** – a medical event in which a small clot or piece of debris from the venous system crosses over to the atrial system creating a condition where blood flow in the artery is blocked.
- **Patent Foramen Ovale (PFO)** – a term used to describe a small hole in the section of the atrial septum that is called the Foramen Ovale.
- **Perforation of vessel or myocardium** – a tear in a blood vessel or the heart.
- **Probe** – a flexible, tube-like medical instrument designed to enter different body cavities.
- **Pulmonary Arteries** – major blood vessels that direct blood from the heart to the lungs.
- **Stroke** – an abrupt onset of neurological symptoms caused by decreased blood flow or bleeding in the brain.
- **TransEsophageal (TEE)** – an ultrasound (sound waves) test to visualize the heart and hole.
- **Thromboembolus** – a blood clot within a blood vessel.
- **TIA** – (transient ischemic attack) a transient lack of oxygen to the brain.
- **Transcatheter Hole Closure**- a less invasive procedure (compared to open heart surgery) used to close heart holes using catheters.

- **Valsalva maneuver** – term used to describe a condition created by the patient when they block exhalation and increase pressure in the chest cavity by contracting the muscles of the stomach and chest. Typically, many people perform a valsalva maneuver when they have a bowel movement.
- **Valvular regurgitation** – an abnormal backward flow of blood through a valve.
- **Ventricle** – the lower two chambers (right and left) of the normal heart.

This guide was prepared by Nitinol Medical Technologies, Inc. It is based on input and guidance from Physicians and Clinical Staff throughout the United States. NMT wishes to thank them for their contributions. However, this guide is not a replacement for speaking with your physician. We recommend you write down questions for your doctor on a separate piece of paper.

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