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Cardiothoracic Surgical Trials Network

NEUROPROTECTION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT

MANUAL OF PROCEDURES



Sponsored By NHLBI, NINDS, CIHR

CT Surgical Trials Network Research Group

Data Coordinating Center

InCHOIR

Icahn School of Medicine at Mount Sinai

New York

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TABLE OF CHANGES

Revision	Section	Change	Reason	Implementation Timeline	Page
2.0	Cover Page, Headers	Changed Date Revised to May 2015 and Rev to 2.0	MOP Update	N/A; Administrative Change	All
2.0	Throughout	Administrative Changes	MOP Update	N/A; Administrative Change	All
2.0	Definitions, Acronyms, and Abbreviations	Added additional definitions, acronyms, and abbreviations	MOP Update	N/A; Administrative Change	All
2.0	Trial Schema	Added Rev 2.0 trial schema	MOP Update	Applies at the time of IRB/REB approval of Rev 2.0	11
2.0	Regulatory Documentation	Updated listing of Regulatory Documents and required staff on DOA Log	Regulatory Update	N/A; Administrative Change	12-16
2.0	Regulatory Documentation	More detail added to changes in study personnel requirement	Regulatory Update	N/A; Administrative Change	16
2.0	Investigator And Study Personnel Training	Rev 1.0 run-in cases language revised and rev 2.0 language added	Study Update	Applies at the time of IRB/REB approval of Rev 2.0	19-20
2.0	Investigator And Study Personnel Training	Collection of Filter content training details revised	Study Update	Applies to both Rev 1.0 and 2.0 patients	20
2.0	Recruitment	Study population recruitment changed to 535 patients, inclusion of CardioGard device arm, and enrollment period increased to 24 months	Study Update	Applies at the time of IRB/REB approval of Rev 2.0	22

Revision	Section	Change	Reason	Implementation Timeline	Page
2.0	Screening & Eligibility Criteria	Pre-screen failure form changed to screening registration form and 'race, ethnicity' added to the compliant language	Regulatory Update	Applies to both Rev 1.0 and 2.0 patients	22-23
2.0	Eligibility Criteria	Added pacemaker considerations to ensure MRI compatibility	To ensure that study inclusion/exclusion criteria are met	Applies to both Rev 1.0 and 2.0 patients	24
2.0	Medical History	Added pacemaker considerations to ensure MRI compatibility	To ensure that study inclusion/exclusion criteria are met	Applies to both Rev 1.0 and 2.0 patients	28
2.0	Medications	All medications collected pre-randomization changed from 7 to 30 days; Day 7 collection of analgesics & psychopharmacological meds added	Study Update	Applies at the time of IRB/REB approval of Rev 2.0	28
2.0	Transesophageal Echocardiogram	Content updated to reflect what is being collected in the EDC	Study Update	Applies to both Rev 1.0 and 2.0 patients	29
2.0	Diffusion Weighted MRI	Added anxiolytic recommendation and pacemaker considerations regarding ensure MRI compatibility	To ensure study endpoint capture	Applies to both Rev 1.0 and 2.0 patients	30
2.0	CAM Assessment	Assessment at baseline included	Study Update	Applies at the time of IRB/REB approval of Rev 2.0	32
2.0	Randomization	More detail information provided on the randomization procedure	EDC clarification	Applies to both Rev 1.0 and 2.0 patients	32
2.0	Surgical Procedure	Language now includes CardioGard device use	Study Update	Applies at the time of IRB/REB approval of Rev 2.0	31

Revision	Section	Change	Reason	Implementation Timeline	Page
2.0	Embol-X Devices	More details provided on sizers, distribution, and preparation processes for use and analysis	Study Update	Applies to both Rev 1.0 and 2.0 patients	31-34
2.0	CardioGard Device	Details provided about the device	Study Update	Applies at the time of IRB/REB approval of Rev 2.0	35
2.0	Hospitalization	Event driven hospitalization data captured in the EDC updated	EDC update	Applies to both Rev 1.0 and 2.0 patients	37
2.0	Monitoring	Source documentation table updated	EDC Update	Applies to both Rev 1.0 and 2.0 patients	41-45
2.0	Informed Consent	Investigational product language removed	Regulatory Update	Applies to both Rev 1.0 and 2.0 patients	46
2.0	Trial Roster	DCC contacts revised	Trial Conduct	Applies to both Rev 1.0 and 2.0 patients	48-49
2.0	Device Accountability Logs	Device accountability logs updated	MOP Update	Applies to both Rev 1.0 and 2.0 patients	57-58
2.0	Device Training	Device training attestation form updated	MOP Update	Applies to both Rev 1.0 and 2.0 patients	59
2.0	Embol-X Filter IFU	Added as Appendix J	MOP Update	Applies to both Rev 1.0 and 2.0 patients	68
2.0	CardioGard IFU	CardioGard Emboli Protection Cannula IFU included as Appendix K	MOP Update	Applies at the time of IRB/REB approval of Rev 2.0	81
2.0	Epi-Aortic Scanning Acquisition Protocol	Added as Appendix L	MOP Update	Applies to both Rev 1.0 and 2.0 patients	89
2.0	Treating Physician Contact Information Form	Added as Appendix M	MOP Update	Applies to both Rev 1.0 and 2.0 patients	91

Revision	Section	Change	Reason	Implementation Timeline	Page
2.0	MRI Incidental Findings	Incidental Findings form included	MOP Update	Applies to both Rev 1.0 and 2.0 patients	93
2.0	BIOTRONIK MRI-Compatible Pacemaker Information	Added as Appendix O	MOP Update	Applies to both Rev 1.0 and 2.0 patients	95
2.0	MEDTRONIC MRI-Compatible Pacemaker Information	Added as Appendix P	MOP Update	Applies to both Rev 1.0 and 2.0 patients	108
3.0	Throughout	Updated Rev to 3.0 and date of Rev to April 2016; made administrative updates	MOP Update	N/A; Administrative Change	All
3.0	Investigator and Study Personnel Training	Added information on how to train additional surgeons for the surgical device run in cases	For clarification	N/A; Administrative Change	23
3.0	Investigator and Study Personnel Training	Clarified Appendix location for run in case training attestation form (Appendix E)	For clarification	N/A; Administrative Change	23
3.0	On-line Training Courses	Removed	Protocol Training conducted via teleconference	N/A; Administrative Change	25
3.0	Eligibility Criteria	Recommendation for all sites to utilize their institutional MRI checklist	For clarification	Applies to all study patients	27
3.0	Eligibility Criteria	Removed mention of MRI-compatible pacemaker	To align with Protocol Rev 3.0	Applies at the time of IRB/REB approval of Rev 3.0	27
3.0	Data collection overview	Clarified when randomization will occur	For clarification	Applies to all study patients	30

Revision	Section	Change	Reason	Implementation Timeline	Page
3.0	Data collection overview	More details provided on data collection for patients who are unable to return for follow up study visits	MOP Update	Applies to all study patients	30
3.0	Medical History	Removed mention of MRI-compatible pacemaker	To align with Protocol Rev 3.0	Applies at the time of IRB/REB approval of Rev 3.0	31
3.0	Medications	Clarified baseline and follow up medication collection	To align with Protocol Rev 3.0	Applies at the time of IRB/REB approval of Rev 3.0	31-32
3.0	Physical Exam	Update on source documentation	MOP Update	Applies to all patients	32
3.0	Physician Exam	Updated list of study personnel that can conduct a physical exam	MOP Update	Applies to all patients	32
3.0	Preoperative Cardiac Catheterization	Clarification on performance of CT Angiography within 3 days of randomization	For clarification	Applies to all patients	33
3.0	MRI Considerations	Removed mention of MRI-compatible pacemaker	To align with Protocol Rev 3.0	Applies at the time of IRB/REB approval of Rev 3.0	33
3.0	Modified Rankin and NIHSS	Added that sites are encouraged to have blinded assessors	Per DSMB recommendation	Applies to all patients	34
3.0	Modified Rankin and NIHSS	Added details on administration of NIHSS for hearing and visual impaired participants	MOP Update	Applies to all patients with hearing impairment	34-35
3.0	Quality of Life Assessments	Clarified collection schedule	MOP Update	Applies to all patients	35
3.0	Barthel Index	Added timeline of when Barthel Index should be	To align with	Applies to all	35

Revision	Section	Change	Reason	Implementation Timeline	Page
		administered	Protocol Rev 3.0	patients	
3.0	Standardization of Surgical Procedure	Added new allowed concomitant procedures	To align with Protocol Rev 3.0	Applies at the time of IRB/REB approval of Rev 3.0	36
3.0	Standardization of Surgical Procedure	Clarified unplanned procedure collection	MOP Update	Applies to all patients	37
3.0	Embol-X Intra-aortic Filter	Clarified Appendix location for Embol-X Sizers Instructions for Use(Appendix I)	For clarification	Applies to all patients	37
3.0	Embol-X Access Device/Aortic Cannula	Clarified Appendix location for Embol-X Access Device/Aortic Cannula Instruction for Use (Appendix F)	For clarification	Applies to all patients	37
3.0	Embol-X Intra-aortic Filter	Clarified Appendix location for Embol-X Intra-aortic Filter Connected with Embol-X Introducer Sheath (Appendix H)	For clarification	Applies to all patients	38
3.0	Embol-X system Instruction for Use	Clarified Appendix location for Embol-X system Instruction for Use (US Sites Appendix J & Canadian Sites Appendix G)	For Clarification	Applies to all patients	39

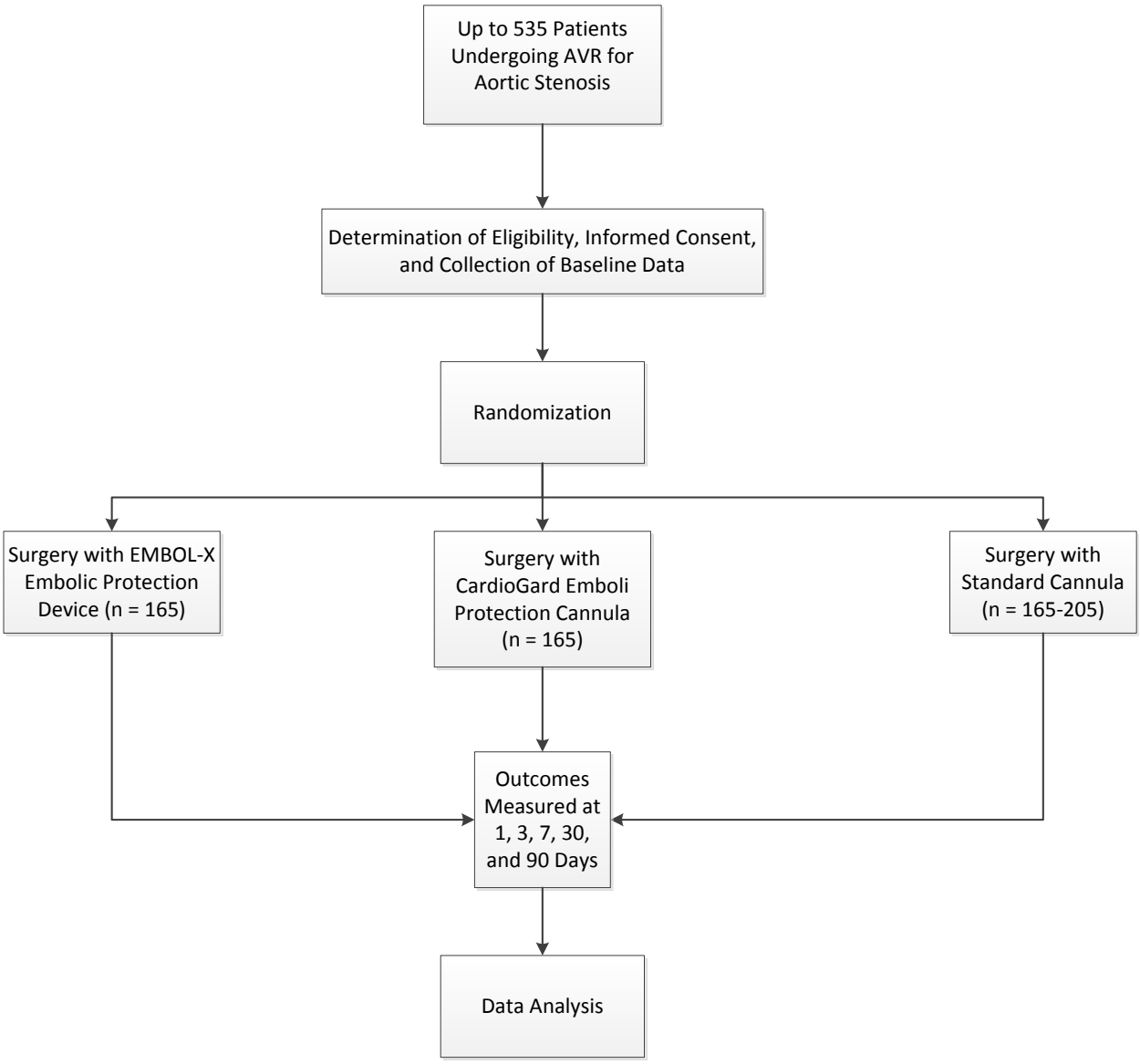
Revision	Section	Change	Reason	Implementation Timeline	Page
3.0	CardioGard Emboli Protection Cannula	Clarified Appendix location for CardioGard Emboli Protection Cannula Instruction for Use (Appendix K)	For clarification	Applies to all patients	39
3.0	Study Completion and Investigator Statement	Added details on Early Termination	MOP Update	Applies to all patients	44-45
3.0	Appendix A	Updated CTSN DCC Trial Roster and Contact Information	MOP Update	N/A: Administrative change	53
3.0	Appendix D	Updated Device Accountability Log	To provide most recent version for use	Applies to all patients	61
3.0	Appendix E	Added CardioGard device to device training attestation form	MOP Update	Applies to all patients	65
3.0	Appendices O and P	Removed MRI-compatible pacemaker descriptions	To align with Protocol Rev 3.0	Applies at the time of IRB/REB approval of Rev 3.0	101

DEFINITIONS, ACRONYMS, AND ABBREVIATIONS

ACGME	Accreditation Council for Graduate Medical Education
AE	Adverse event
AS	Aortic stenosis
AVR	Aortic valve replacement
CABG	Coronary artery bypass graft
CAM	Confusion Assessment Method
CFR	Code of Federal Regulations
CIHR	Canadian Institutes of Health Research
CPB	Cardiopulmonary Bypass
CRF	Case report form
CTA	Clinical Trial Agreement
CTSN	Cardiothoracic Surgical Trials Network
CV	Curriculum vitae
DCC	Data and Clinical Coordinating Center
DOA	Delegation of Authority
DSMB	Data and Safety Monitoring Board
DWI	Diffusion-weighted imaging
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ICU	Intensive care unit
IFU	Instructions for Use
InCHOIR	International Center for Health Outcomes & Innovation Research
IRB	Institutional Review Board
JVD	Jugular Venous Distention

MRI	Magnetic resonance imaging
NHLBI	National Heart Lung & Blood Institute
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
PDC	Protocol Development Committee
PI	Principal Investigator
PIPEDA	Personal Information Protection and Electronic Act
QoL	Quality of life
REB	Research Ethics Board
REDCap™	Research Electronic Data Capture application
SAE	Serious adverse event
T	Tesla
TEE	Transesophageal echocardiogram
TIA	Transient ischemic attack
UP	Unanticipated problem

Trial Schema (Protocol Rev 3.0)



I. Clinical Centers

This trial will be conducted at multiple clinical sites in the United States and Canada. The sites are chosen from a pool of highly qualified cardiothoracic surgical centers with the required surgical volume and infrastructure, including magnetic resonance imaging (MRI) capabilities, to conduct this trial.

II. Regulatory Documentation

Each clinical site is required to complete the trial regulatory documents and submit them to the Data and Clinical Coordinating Center (DCC) at the International Center for Health Outcomes and Innovation Research (InCHOIR) located at the Icahn School of Medicine at Mount Sinai, New York, New York prior to site initiation. Regulatory documents are to be emailed to the DCC regulatory staff (Appendix A) at ctsn.regulatory@mountsinai.org or faxed to 212-731-7346.

A Clinical Trial Agreement (CTA) with the DCC must be fully executed prior to initiation and enrollment *with no exceptions*.

A. *Maintenance of Regulatory Documents*

The site will maintain a regulatory binder for the protocol that must be updated as new revisions of study documents are made and approvals are renewed.

The following documents are required to be in place and/or submitted to the DCC before the site will be open to enrollment, *with no exceptions*:

- CTA with the CTSN DCC: InCHOIR, Department of Population Health Science and Policy, Icahn School of Medicine at Mount Sinai
- Institutional Review Board (IRB)/Research Ethics Board (REB) approval for protocol, informed consent document, HIPAA authorization (for US sites)
- Protocol Signature Page/Document Approval Form signed by the Principal Investigator (PI)
- Completed Delegation of Authority Log (DOA Log)
- Signed and dated CVs for all staff on DOA Log
- Current licenses for all appropriate staff on DOA Log
- Signed CTSN Conflict of Interest Statements) for all staff on DOA Log
- Privacy training (HIPAA or PIPEDA[1]) and Human Subjects training documentation (as required by local institutional guidelines) for all staff on DOA Log
- IRB/REB roster
- Federal Wide Assurance (FWA) number and expiration date
- Clinical Center Laboratory Certification

- Laboratory Normal Ranges
- Dangerous Goods Certification Training for appropriate staff
- NIH Stroke Scale (NIHSS) Training Certification, Modified Rankin Scale Training, and Barthel Index Certification for delegated staff
- Coordinator Neurocognitive Battery and CAM Assessment Training Certification
- Electronic data capture system (EDC) Training Attestation Forms for all study staff listed on the DOA Log with data entry responsibilities
- Site Initiation Documentation for all staff on DOA Log
- Surgical Procedure Training Attestations
- MRI Lab Image Certification
- Surgical and Neurology Investigator Certifications

After site initiation, sites must maintain their regulatory files to include updates to all of the above documentation as they occur, as well as additional documentation. Post-site initiation documentation includes the following:

- Copies of all revisions of the protocol
- Copies of all Protocol Signature Pages/Document Approval Forms
- Conflict of Interest Statements
- Copies of all IRB/REB approved versions of the informed consent document
- Informed Consent Log
- Protocol Consent Version Tracking Log
- Copy of the device Instructions for Use (IFU)
    - Edwards Embol-X System
    - CardioGard Cannula
- All IRB/REB correspondence, including emails
- IRB/REB approvals for the protocol and informed consent
- CTA(s)
- Signed and dated CVs for all study staff (updated every 2 years)
- Site Visit Log
- Site DOA Log

- Correspondence with DCC
- Specialized Training Certifications:
    - HIPAA or PIPEDA Training, GCP and Human Subjects Protection Training for all staff
    - IATA/Dangerous Goods Training
    - MRI Lab Image Certification
    - EDC Training
- Patient Contact Log
- Serious Adverse Events Log
- Manual of Procedures (MOP)
- Source Document Worksheets/Case Report Forms (CRFs)

For sites participating in more than one CTSN trial, a cross-study binder may be maintained that will contain documents applicable to more than one study. This may include CVs, licenses, training documentation, IRB/REB roster, and laboratory information. This will assist the site in maintaining up-to-date records and will assist the DCC monitors in reviewing the files efficiently. The study-specific regulatory binders should contain a note to file in each section where the cross-study binder will hold those documents (e.g., CVs) explaining the location of the documents.

The clinical site should follow the procedures listed below in their regulatory documentation:

- Ensure that for each section regarding personnel (CVs, licenses, trainings, site initiation, etc.) each staff member listed on the DOA is represented.
- Ensure that IRB/REB approvals (including those for recruitment materials) are all on file in date order.
- Ensure that laboratory certifications, IRB/REB roster, and FWA information remain current.
- Verify that the most current versions of trial documents, e.g., protocol, IFUs, MOP, consent forms, are stored in the regulatory binder. Old versions may be stored separately as long as a note to file with the archived versions' location is present.

Signature and DOA Logs should be drafted as follows:

- Staff titles should be consistent with the IRB/REB submission. Be careful to avoid titles such as "Co-PI" and "Sub-PI". Each study site has only one PI. The DCC recognizes investigators either as a PI or as a Sub-Investigator.
- PI responsibilities on the DOA Log must include the PI Oversight of All Study Tasks option.
- Make sure that the staff member listed for each task on the DOA Log is qualified by education, experience, and training for each delegated task as shown by the CV and, where applicable,

license of the study team member. Additionally, each task should be delegated to more than one person so that back-up is available for each type of assessment.

- Make sure that only the staff member delegated for each task on the DOA Log is conducting the study assessments.
- Each site DOA Log must include a neurologist (delegated to assess AEs), a radiologist (delegated as supervising the acquisition of the DWI-MRI) and a perfusionist (delegated for perfusion tasks).

B. *IRB/REB Requirements*

Sites are required to follow their institutional guidelines for obtaining initial approval by the IRB/REB and for submitting continuing reviews to the IRB/REB submission. The DCC will send clinical centers an email reminder 90 days prior to IRB/REB approval expiration date to help sites plan the annual renewal of the study accordingly. A copy of the IRB/REB letter of re-approval must be forwarded to the DCC and filed in the site regulatory binder upon receipt by the clinical site study team.

The informed consent must be re-approved in accordance with the clinical center's IRB/REB polices or at least annually.

The DCC will provide the sites with Data and Safety Monitoring Board (DSMB) protocol approval letters and all applicable correspondence during the course of the trial.

C. *Consent Form Modifications*

Clinical centers are required to submit any consent form modifications to the DCC for review and approval prior to the IRB/REB submission at the clinical center. Consent form modifications are to be made using the tracked changes mode on the DCC approved consent template and emailed to the DCC regulatory staff for review at ctsn.regulatory@mountsinai.org.

The DCC understands that revisions to the consent form may be required to satisfy institutional IRB/REB requirements and requests. For example, an IRB/REB may request that the consent form include additional language or remove PDC approved language. If required by their IRB/REB, clinical centers are allowed to remove or add additional consent language with DCC approval of proposed changes. The DCC recommends not volunteering any additional language when not specified by the IRB/REB. **Any consent form modifications requested by the IRB/REB are to be reviewed and approved by the DCC prior to re-submitting the consent form to the IRB/REB.**

D. *Patient Compensation*

During the consent process a patient might ask about compensation for trial participation. Although the consent form template states participants will not receive compensation, the clinical center trial budget is provided as a "per patient" total amount allowing each clinical center to determine how funds are allocated for this trial. Please review your institutional policy on study participant compensation.

Providing compensation, such as travel reimbursement or gift cards, might help with enrollment and patient retention and is encouraged by the DCC.

E. *Changes in Study Personnel*

The DCC regulatory staff must be informed of any personnel changes in PI, Sub-investigator, and/or coordinators in writing within 15 business days of the addition of new staff. An email correspondence is an acceptable form of written communication. The site should inform the DCC of any deletions from study staff immediately, especially in cases in which access to the EDC should be disabled.

Complete documentation for the new study personnel should be emailed to ctsn.regulatory@mountsinai.org or faxed to 212-731-7346.

Documentation should include:

- Role in the Study
- Complete contact information including telephone, fax, email address, and mobile number
- Curriculum vitae (signed and dated within 2 years)
- GCP and HIPAA or PIPEDA certification as required by the local site
- Clinical Trial Agreement, as applicable (e.g., to reflect a change in PI)
- Specialized Training Certification, as applicable
- Conflict of Interest Statement
- Protocol Training Attestation Form
- Signature on DOA Log

III. STUDY COMPLIANCE

A. *Site Certification*

Clinical sites will complete an electronic site feasibility survey via "REDCap." Information captured in the survey will help assess the experience and resources of the site to conduct the trial. Sites must provide the volume of aortic valve replacements, aortic valve replacements with coronary artery bypass grafting and aortic valve replacements with mitral annuloplasty performed by the PI. The sites must also provide information on their MRI capabilities.

In addition to the MRI information submitted via "REDCap," each clinical site is required to submit a qualifying MRI imaging study using the acquisition protocol developed by the MRI Core Lab to be certified prior to being open to enrollment.

B. *Investigator Certification*

The protocol outlines specific requirements for all surgical and neurologic investigator participation in the trial. Cardiothoracic surgeons and neurologists may not participate as investigators in the trial without meeting the minimum requirements cited in the protocol under Qualifications and Training.

To qualify as a surgical investigator, the surgeon must have performed at least 10 aortic valve replacement procedures annually (averaged over a 2 year period).

To qualify as a neurology investigator, the neurologist must be either currently participating in an ACGME-accredited neurology residency or be board certified in neurology. To confirm that the investigator requirements have been met, the clinical site must submit a Certification Form for each surgical and neurology investigator to the DCC for review prior to initiation.

All investigators (surgical and neurology) will be trained by the DCC on the clinical trial protocol prior to site initiation. Only investigators with documented participation in protocol training may participate in this trial. It is the responsibility of the clinical site PI to oversee the ongoing performance of all other participating surgical and neurology investigators at their site over the course of the trial.

C. *Good Clinical Practices (GCP)Certificate, HIPAA or other Privacy Certificate & Patient Confidentiality*

All investigators, coordinators and other study staff members who are involved in the care of study patients, and/or research data collection must submit documentation that they have successfully completed their institutionally required HIPAA (US sites only), PIPEDA (Canadian sites only), GCP or Human Subjects Protection training to the DCC prior to site initiation.

Confidentiality of all patient records will be maintained according to HIPAA and PIPEDA guidelines. All unique patient and hospital identifiers will be removed prior to review of source documentation. Study Investigators, site IRBs/REBs, the DCC (InCHOIR), the Event Adjudication Committee (EAC), the NHLBI, and the Data and Safety Monitoring Board (DSMB) may review source documentation for enrolled patients as necessary to ensure patient safety.

D. *Conflict of Interest Statements*

Conflict of Interest Statements will be collected from all study investigators to ensure that no investigator may exert undue influence that may bias the trial. Any conflict of interest identified must be explained in writing and will be reviewed by the NIH and managed in compliance with 21 CFR 54 and 42 CFR 50(f). Conflict of Interest Statements will be updated as potential new conflicts arise and no less than annually.

E. *Protocol Deviations*

Efforts to maximize adherence to the study protocol will be made through careful and comprehensive training, early review of study data submitted via the EDC system, and routine communication with all

site investigators. Despite the best efforts of the clinical investigators, protocol deviations and/or violations may occur. These deviations and/or violations may include, but are not limited to, enrolling an ineligible study participant, failing to properly obtain informed consent, failing to maintain IRB/REB and related study documents, administering the wrong treatment, and performing incomplete or out of window assessments.

All protocol deviations and violations are to be submitted to the DCC through the EDC within 5 business days of the PI becoming aware of the occurrence. These forms will be reviewed by the DCC on a monthly basis.

The following information will be documented on the Protocol Deviation/Violation Reporting Case Report Form (CRF) in the EDC:

- Date of occurrence
- Date site aware of occurrence
- Participant ID
- Detailed description of violation/deviation
- Steps taken to resolve the particular occurrence

Once completed and submitted by the site coordinator, the Protocol Deviation/Violation CRF is reviewed by a member of the trial team at the DCC. The DCC will contact the site coordinator, when necessary, to address the deviation/violation and discuss the steps taken to resolve the occurrence. The CRF is released back to the clinical site following DCC review and signature for PI signature.

All protocol deviations and violations will be listed in the protocol-specific Deviation/Violation Log. This log must be maintained at each site. For protocol deviations and violations submitted to the local IRB/REB, the log will indicate the date of submission of the deviation or violation to the local IRB/REB and the date of IRB/REB acknowledgement. Clinical sites are to follow their institutional policies for reporting protocol deviations and violations to the local IRB/REB.

The DCC will notify appropriate parties, including the study site PI, NHLBI, NINDS, CIHR, and/or DSMB, of relevant violations.

IV. INVESTIGATOR AND STUDY PERSONNEL TRAINING

All clinical site investigators, coordinators and study team members are expected to familiarize themselves with the specifics of the protocol prior to the site initiation conference call. Study team members joining the trial following site initiation may only conduct study activities once all role-specified trainings have been completed. This will ensure that the investigators and all members of the study team are thoroughly familiar with the clinical trial protocol and study role responsibilities. Trainings will be conducted using a variety of platforms, including in-person demonstrations, on-line training courses and information webinar sessions.

A. *Surgical Device Run-In Case(s)*

For sites initiating the trial under Protocol Rev 1.0:

Each clinical site is required to conduct 2-3 run-in cases using the Embol-X Protection Device under the guidance of an Edwards Lifesciences clinical specialist prior to randomizing the first trial patient. Edwards Lifesciences or a designee will provide on-site training on the standard preparation and use of the Embol-X Protection Device. The site coordinator will coordinate the timing of these cases with the Edwards Lifesciences representative to attend the AVR case(s) using the Embol-X device.

For sites transitioning from Rev 1.0 to Rev 2.0:

Clinical sites will be required to conduct 2-3 run-in cases using the CardioGard device ***prior to transitioning to Rev 2.0 of the protocol***. A clinical specialist or a designee from CardioGard will provide on-site training on the standard preparation and use of the CardioGard cannula and inline filter at each site prior to the site randomizing the first Rev 2.0 patient. In addition to the proctored cases, the clinical specialist will also train the local perfusionists on pump set-up for the device.

For sites initiating the trial under Protocol Rev 2.0:

Each clinical site is required to conduct 2-3 run-in cases each using the Embol-X Protection device and the CardioGard cannula. A clinical specialist from Edwards Lifesciences and a clinical specialist from CardioGard or a designee will be on site prior to randomization of the first trial patient. Edwards Lifesciences or a designee will provide on-site training on the standard preparation and use of the Embol-X Protection Device and CardioGard or a designee will provide on-site training on the use of the CardioGard Cannula as well as on-site training with site perfusionists on pump use for the cannula. The site coordinator will coordinate the timing of these cases and make arrangements with the companies' clinical representatives to attend.

These proctored run-in procedures will **NOT** be included in the study; therefore, these patients will not be followed or have data collected post-operatively for study purposes. A signed copy of run-in training attestation (Appendix E) for all surgical investigators and surgical team members must be e-mailed to ctsn.regulatory@mountsinai.org .

After the initial Edwards Lifesciences and/or CardioGard training, the certified clinical site surgeons may provide oversight and training for additional surgeons' run-in cases. In the event an eligible patient is identified for trial participation and the attending surgeon is not yet trained for the trial intervention, the patient may be consented for trial participation. A trial certified clinical site surgeon must be present at the time of randomization and will oversee the investigational portion of the operation. This case may then count as a run-in case for the attending surgeon.

B. *Collection of Filter Content Training*

Filter collection and preparation for analysis training will also be conducted by the clinical specialists from Edwards Lifesciences and CardioGard for their respective devices during the scheduled run-in proctored cases. An overview of the filter collection and preparation for analysis procedure, including a review of the Core Laboratory will be conducted by the DCC during the site initiation conference call or via the site initiation online webinar. Additional information on filter preparation is available in the Filter Content Analysis Core Laboratory Manual.

C. *Neurocognitive Battery Training*

Neurocognitive assessments outlined in Appendix I of the protocol can only be administered by study personnel who have received in-person training in the full battery and are certified by the CTSN Neurocognitive Core Laboratory. The CTSN Neurocognitive Core Laboratory will train and certify the site designated study coordinators in the administration of the neurocognitive testing. The certificate of training provided by the core lab must be filed in the site regulatory binder and a copy should be forwarded to the DCC regulatory staff at ctsn.regulatory@mountsinai.org.

D. *NIH Stroke Scale (NIHSS) Training*

All study personnel responsible for administering the NIHSS, as noted on the DOA Log, must receive on-line training and certification. Training and certification will be completed using the following website: http://www.nihstrokescale.org. The NIHSS certificate is to be printed and filed in the site regulatory binder at the completion of training. Copies of all NIHSS certificates for the clinical center are to be emailed to ctsn.regulatory@mountsinai.org.

E. *Modified Rankin Scale Training*

All study personnel responsible for administering the Modified Rankin Scale, as noted on the DOA Log, must receive on-line training. Training will be completed using the following website: https://secure.trainingcampus.net/uas/modules/trees/windex.aspx?rx=rankin-asa.trainingcampus.net. Documentation of Modified Rankin Scale training completion must show the trainee's printed full name, date and signature and is to be printed and filed in the site regulatory binder at the completion of training. Copies of all Modified Rankin Scale certificates for the clinical center are to be emailed to ctsn.regulatory@mountsinai.org.

F. *CAM Assessment Training*

The CTSN Neurocognitive Core Laboratory will train the study coordinators in the administration of the Confusion Assessment Method (CAM) testing in two forms: the CAM-ICU for intubated or non-verbal patients and the CAM-3D for verbal patients. The CAM assessments outlined in the protocol can only be administered by study personnel who have received training and have been certified by the Core Laboratory staff to perform the assessments. The certificate of training provided by the core lab

must be filed in the site regulatory binder, and a copy should be forwarded to the DCC regulatory staff at ctsn.regulatory@mountsinai.org.

G. *Electronic Data Capture (EDC) System Training*

All study team members who are responsible for entering data are required to complete electronic data capture system training. EDC training is conducted using computer-based platforms, specifically webinars and an on-line training course. Study team members are only required to complete EDC training once, either through a webinar or on-line training course.

Webinar attendance or attestation of on-line training course completion will be the basis for obtaining access to the EDC training site. Study team members are required to show proficiency on the EDC training site before access to the production EDC site is granted. An attestation documenting completion of EDC training site requirements is required. Once the DCC has received a study team member's attestation, completion of training tasks are confirmed by the DCC and the individual user will be granted access to the trial production site.

Please note: EDC user names and passwords must be kept confidential and not shared among study personnel.

H. *Site Initiation*

In order to be **eligible** for site initiation, the following requirements must be met:

- IRB/REB Approval for Protocol and Consent Form
- Fully Executed Contract
- Regulatory Documentation Submitted to the DCC (see Section II-A)
- Training Documentation Submitted to the DCC (see Section II-A)
- Surgical Device Run-In Training Completion

Representatives of the DCC (listed in Appendix A) will conduct the site initiation prior to enrollment of the first patient for each site. The PI, lead neurologist investigator, and the trial coordinator(s) are all required to attend the site initiation conference call. Participation is encouraged and welcomed for all other study team members.

The site initiation focus is on a review of the site specific regulatory documents, the site's surgical run-in case experiences, and a question and answer session to ensure that site staff understand all aspects of the protocol.

V. RECRUITMENT

A. *Study Population*

Up to 535 patients diagnosed with calcific aortic stenosis (AS) with planned AVR will be randomized to a 1:1:1 ratio of the Edwards Embol-X protection device, the CardioGard Emboli protection cannula or a standard cannula. All patients will be followed for 90 days post-surgery.

B. *Recruitment Strategies*

Enrollment strategies may include presentations at grand rounds, newsletters and mailings to referring physicians of the study hospitals, symposia, and health care events targeted towards this population as well as telephone calls to neighboring health care facilities.

C. *Enrollment Targets*

Following a review of the pre-screening logs with site surgical volumes submitted by each clinical site, the Neuroprotection Trial Operations Committee will determine enrollment targets for each site. The DCC will regularly assess clinical site enrollment against their pre-specified goals using the site metric. When necessary, interventions to facilitate enrollment will be implemented to help increase enrollment at the site and trial level.

The enrollment period is expected to last 24 months.

VI. SCREENING & ELIGIBILITY CRITERIA

A. *Patient Screening*

Prior to approaching a patient to begin the informed consent process, the study personnel will review data on the prospective patient to determine eligibility for inclusion in the trial. This will include a chart review of all the available medical history against the eligibility criteria to assess whether the patient should be approached for participation. Each site will need to follow its institutional policies and procedures for accessing medical information in preparation for research, which typically includes obtaining a waiver for authorization from their IRB/REB.

All pre-screened patients (patients who are not consented) who are not enrolled are recorded in the Screening Registration form. The coordinator will specify all eligibility criteria not met for participation when a patient is not consented due to ineligibility. The data collected are HIPAA and PIPEDA compliant and do not include patient identifiers but do include screening quarter, screening year, age, gender, race, ethnicity, and reason(s) not eligible or not enrolled.

B. *Eligibility Criteria*

Candidates who meet all inclusion criteria and no exclusion criterion as outlined in the protocol will be eligible for the trial regardless of gender, race, or ethnicity. Please keep in mind that certain eligibility

criteria, specifically under exclusion, are contingent on time from enrollment. When evaluating the exclusion criteria, it is important for the coordinator to work closely with the surgical investigator to determine whether it is appropriate for the patient to participate in the trial. It is highly recommended that the site utilize their institutional MRI checklist to rule out any existing conditions that could preclude the completion of the MRI. The study staff reviewing the medical history should also document whether the patient has any history of claustrophobia, ligyrophobia or other concerns that might prohibit the completion of MRI testing during this trial.

An additional consideration for participation must include an evaluation of the patient's ability to return for follow up given post procedure data collection requires an in person visit.

VII. INFORMED CONSENT, HIPAA AUTHORIZATION, RELEASE OF MEDICAL INFORMATION

A. *Informed Consent Process*

Prior to screening, a thorough explanation of the risks and benefits of participating in the study will be outlined by the investigator or designee to the potential study subject. Study personnel will begin the informed consent process as soon as possible during the preoperative evaluation phase for each patient. Timing for the informed consent process must be consistent with the center's institutional IRB/REB and privacy policies, and in accordance with the CTSN guidelines, which require that the consent process must begin at least the day before the surgical procedure. This is to ensure that all subjects will be given adequate time to review the informed consent document and consider participation in the trial. All questions will be answered to the satisfaction of the subject prior to signing the informed consent document. Site source records will include documentation of the informed consent process for each subject. No study specific procedures will be performed prior to signing of the informed consent document.

A patient should be encouraged to have family or other support available during the informed consent process. They should be assured that declining to sign an informed consent document will in no way compromise their care, and that should they consent to participate in the study, they may revoke that consent at any time.

The consent process must be documented in the medical chart and a signed copy of the consent form must be given to the patient. All signed consent forms, including the initial consent and any re-consents, are to be uploaded into the EDC on the patient Screening Registration form. In addition, the investigator must:

- Document any questions addressed with the patient and/or family during the informed consent process in the medical chart
- Confirm that all signatures on the informed consent are complete and dated

- File the original signed informed consent with study participant's research documents

Additional information on documenting the consent process can be found in Section XVI (Monitoring).

B. *Consenting Non-Native Language Speaking Patients*

Clinical sites must abide by local institutional guidelines when approaching a patient who does not speak/read the language in which the consent is written for the informed consent process. Local IRBs/REBs will have guidelines in place that must be followed. For all consented participants who do not speak/read the language of the written consent form, the clinical site must document the information noted in the above paragraph but also specify such information as:

- A brief description of local policy on consenting a patient who does not speak/read the language in which the consent is written;
- A brief description of how this policy was followed in the consent process for the patient;
- The name of the translator and/or anyone else present at the time of consent;
- A statement that the patient was given the opportunity to ask questions and to receive answers about the study in his/her native language.

C. *Consenting Visually Impaired or Low Literacy Level Patients*

Clinical sites must abide by local institutional guidelines in the informed consent process for visually impaired or patients with a low literacy level. As with consenting a speaker of language other than the language the consent is written in, the clinical sites must specify additional information on the consenting process including:

- A brief description of the local policy on consenting patients with visual impairments or literacy challenges;
- A brief description of how this policy was followed in the consent process for the patient;
- The name of the person reading the consent form to the patient and/or anyone else present at the time of the consent process;
- A statement that the patient was given the opportunity to ask questions and to receive answers about the informed consent document as it was read to him or her.

D. *Informed Consent Log*

An Informed Consent Log, which captures the date of consent and the version of consent form used, will be completed for each study participant and uploaded onto the Screening Registration CRF. The log will include date of re-consent, version of consent form used for re-consent and reason for re-consent, if necessary. Should a study participant be re-consented, the updated Informed Consent Log will be uploaded onto the Screening Registration CRF.

E. *HIPAA and Release of Medical Information Forms*

Each site is required to follow their institutional policy for HIPAA Clinical Research Authorization (US sites only) and Release of Medical Information. Consent to authorize release of medical records to the trial investigators, monitors, sponsors (NHLBI, NINDS, CIHR) and the DCC must be obtained for trial participation.

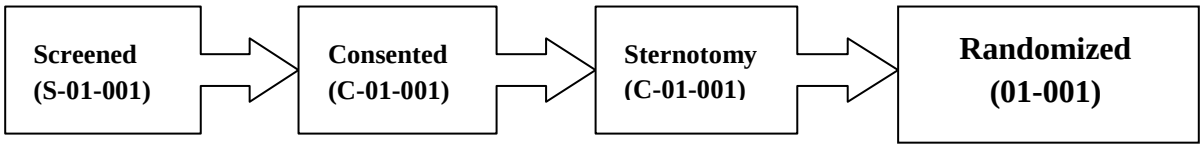
VIII. DATA COLLECTION OVERVIEW

Data collected for this study is outlined in the data collection schedule (of assessments) and data collection sections of the protocol. This section of the Manual of Procedures (MOP) provides supplemental information to help coordinate and complete the assessments collected over the course of the trial.

In order to document investigator oversight in the study, the PI (or a delegated sub-investigator) will sign and date laboratory reports and other source documentation with a note of significant findings as applicable.

A. *Screening and Study Participant Identification Number*

All screened patients and consented study participants will be issued a numeric patient identification number (Patient ID) that will be automatically generated by the EDC following the completion of the required *Screening Registration CRF* fields. The Patient ID will consist of a two digit site number followed by a three digit sequential site specific patient number, e.g., 01-001. Since all patients screened for the trial will be entered into the EDC, the letter "S" will appear before the Patient ID to distinguish those patients that have not been consented. After the patient has been consented, the letter before the Patient ID will change from "S" to "C" in the EDC. Once a patient has been randomized, the Patient ID will lose the "C" and will just have the numeric Patient ID displayed.



All patients entered into the EDC may be filtered by status (screened, consented, and randomized).

All source documentation will be de-identified using the numeric Patient ID, including but not limited to, pre-implant source, index surgical procedure and hospitalization source, adverse event (AE) source and follow-up visits.

B. *Study Visits*

For all study visits, **data collected is to be entered into the EDC within 5 business days.** Event driven data, including AEs, is to be reported via the EDC as outlined in the sections below.

Once a study participant has signed the consent form, the study coordinator should confirm the anticipated date of surgery with the operating surgical investigator. Screening and baseline data collection windows are calculated from the date of randomization. **Randomization will be performed inside the operating room after sternotomy and following confirmation by the surgeon of the patient's eligibility to undergo the intervention in any of the three treatment arms.**

Screening and baseline data collection windows range from within 7 day to 30 days prior to randomization. Screening and baseline data will be collected for every consented study participant regardless of randomization status. Study participants who do not meet randomization eligibility criteria will be entered as screen failures in the EDC. Participants who meet criteria but will not be randomized will have their status entered as such in the Patient Status field on the *Randomization Eligibility CRF*. No additional data will be collected for these participants. Randomized study participants will have data collected pertaining to index hospitalization, any subsequent hospitalizations, index surgical procedure, additional procedures, follow-up visits and AEs.

The date of randomization will be used to calculate the follow-up assessment windows. The EDC will auto-populate the visit window dates when the *Randomization Verification CRF* is completed and saved; these dates will be displayed on each visit folder. Scheduling follow-up appointments with the study participant and collaborating departments should be done with as much notice as possible to prevent scheduling conflicts and to ensure visits are completed within the specified windows. It is acceptable to conduct the study visit over multiple days provided the assessments listed for that visit are completed within window.

For the purposes of this trial, study visits are considered as having occurred if a single data point for the visit is ascertained. When no data is captured for the entire visit, the study visit will be categorized as a missed visit. Data may be gathered from a variety of sources and some data points, such as patient status, do not need to be collected from direct study participant contact.

Each clinical site is required to keep a Patient Contact Log to document any and all mail, e-mail, and telephone correspondence with randomized study participants. Any in-person visit, either standard of care or research, will be documented on the Patient Visit Log. All correspondence and visit details are to be documented in the study participant's record and will be reviewed against the Logs during monitoring visits. The Logs will also be reviewed as part of the remote monitoring procedures on a regular basis.

Every effort should be made to have ALL patients return to your institution for a 30 and 90 day follow up. In the case where a patient is not able to return, the Barthel Index and Modified Rankin Scale can be collected via a phone interview. Quality of life forms can be mailed to the patient with a return envelope for them to complete.

C. *Medical History*

The medical history data that is being captured in this trial will include previous myocardial infarction, myocardial revascularization, stroke, and other comorbidities such as diabetes and peripheral vascular disease. The current medical condition of the patients will also be required at screening.

The study staff is required to review the medical history with the study participant to confirm that the entire history is documented accurately in their record.

D. *Laboratory Assessment*

Chemistry panel, liver function tests, coagulation profile and hematology labs are to be collected following the standard institutional procedures for blood collection and submitted for the local laboratory at the site for analysis. Blood may be drawn from a central venous catheter. All results are to be reviewed, signed and dated by a study investigator. The study investigator will classify any results that are not within his/her institution's respective normal range as either clinically significant (CS) or not clinically significant (NCS). Medical discretion by the study investigator will be used to report any clinically significant abnormal laboratory results.

There will be event driven laboratory values captured to adjudicate AEs.

E. *Medications*

At baseline, all medications the study participant is taking the day of the screening visit will be recorded in the EDC.

Cardiovascular, analgesic and psychopharmacologic medications are collected at Day 7(±3). Categories to be collected include:

- Anti-Alzheimer medications
- Anti-emetics
- Antihistamines (H-1 Blockers)
- Antidepressants
- Anti-anxiety medications
- Anti-cholinergic medications
- Anti-manic medications
- Anti-seizure (anti-epileptic) medications
- Antipsychotics
- Anti-Parkinson medications
- Anti-vertigo medications
- Benzodiazepines
- Cardiovascular medications (specified below)
- COX-2 Inhibitors
- Gastrointestinal medications

- Urinary Incontinence medications
- Muscle Relaxants
- Narcotic Analgesics
- Sleeping medications
- Sedative/Hypnotic medications
- Stimulant medications

During the follow-up period, only cardiovascular medications are collected at each of the study visits identified below and for any associated AE.

Cardiovascular medications of interest for this trial:

- Anti-platelet
- Anti-coagulation
- Beta Blockers
- Diuretics
- Nitrates
- Vasodilators
- Vasopressors and Inotropes Therapies

Cardiovascular medications associated with an AE should be uploaded with AE source documentation on the corresponding AE form.

F. *Physical Examination*

- This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).
- A Physician, PA, or NP is allowed to perform the baseline examination; however, the follow up examination should be conducted by a study staff member who is listed on the DOA Log.

Reminders:

- All physical exam findings including jugular venous distention (JVD), peripheral edema, and murmurs must be clearly documented in the patient's record if assessed on the date of exam.
- Lack of documentation for clinical variables does not translate into a negative finding. Negative findings must be clearly documented in the patient's record.

G. *Preoperative Cardiac Catheterization*

The date and whether the aortic valve was crossed with a catheter or wire will be collected on any clinically indicated cardiac catheterization performed within 30 days prior to randomization. **Cardiac catheterization performed within three days (72 hours) prior to randomization excludes a patient from study participation.**

CT angiography done within 3 days of randomization does NOT exclude the patient from study participation.

H. *Transesophageal Echocardiogram*

Images from the standard of care intraoperative transesophageal echocardiogram (TEE) will be collected and used to evaluate the inner diameter of the aorta and for the core lab to assess the presence of intracardiac thrombi and/or endothelial disruptions on the interior of the aorta. The coordinator will upload the de-identified images via the EDC for interpretation by the Echo Core Laboratory, located at the Massachusetts General Hospital, under the direction of Dr. Judy Hung.

I. *Epi-aortic Scan*

Epi-aortic scanning will be performed twice during the initial surgical intervention using the epi-aortic acquisition protocol (Appendix L) developed by the Echo Core Laboratory. Scanning will be conducted before placement of the cannula for aortic lumen sizing and assessment of atherosclerosis degree then after removal of the cannula to determine the presence or absence of aortic lesions. The coordinator will upload the epi-aortic scan via the EDC for interpretation by the Echo Core Laboratory.

J. *Diffusion-Weighted (DW) MRI*

All patients will undergo a DW 1.5 or 3.0 Tesla MRI at 7 (± 3) days post-surgery to assess for the presence of brain lesions. The number and volume of brain lesions will be documented. The University of Pennsylvania MRI Core Lab will develop the acquisition protocol, a manual of operations, and train and certify the lab personnel at each site to perform this task. The site will make every effort to ensure that all study MRIs are performed using the same machine. The MRI will be uploaded to the EDC for transmission to the Core Lab who will read and adjudicate all outcome data.

MRI Considerations

Investigators should consider premedicating patients, as clinically indicated, with anxiolytic medications before performing the MRI in an effort to minimize anxiety or panic attacks and maximize patient completion of the MRI scan.

Patients with pacemakers that are implanted during the index procedure will not be able to perform the MRI. If a patient leaves the OR with epicardial pacing wires, every effort must be made by the surgical staff to remove these wires in their entirety. If a patient's epicardial pacing wires are clipped and not fully removed the patient may not be able to perform the MRI.

Interpretation of MRI Findings

If, at the time of the research MRI, a patient has new or exacerbated clinical symptoms that may be associated with a neurological event, the site may have an institutional neuroradiologist interpret the research images for the purpose of clinical management. Additionally, each site will complete a treating physician contact information document (Appendix M) for the MRI core lab to provide a report of any incidental findings (Appendix N) discovered in the analysis of the research MRI.

K. *Neurological Assessments*

Only study team members certified and identified on the DOA Log may administer the neurological assessments for this trial. Please follow the instructions for completing the Neurocognitive Testing located in Appendix I of the protocol.

The neurocognitive batteries used in this trial have been validated in English, Spanish, and French. For patients who do not speak English, Spanish, or French as a first language, completion of the neurocognitive batteries is not required. These patients should not be precluded from participating in the trial.

The neurocognitive batteries will take approximately 1 hour to complete and will be recorded using a digital audio recorder. The timing of the testing should be considered in view of other visit related activities. Optimally, the study participant should be rested. Results from these tests will be independently scored by investigators from the Duke University Neurocognitive Core Laboratory.

Quality assurance will be performed on the recordings and data (as detailed in the Neurocognitive Core Lab's "Nurses' Cognitive Training Directive"). All testing batteries are uploaded through the EDC and will be stored at Duke University Medical Center until the completion of study data analyses at which point the audio recordings will be destroyed. Prior to that point, the recordings will be destroyed upon receipt of a formal request for destruction from the Data Coordinating Center or from an enrolled patient.

L. *NIHSS and Modified Rankin Scale*

Only certified members of the study team may perform the NIHSS and the Modified Rankin Scale. Whenever practical, sites are encouraged to have clinicians blinded to treatment assignment perform these assessments. These neurological assessments are conducted during baseline and at the designated protocol follow-up visits. Following a neurological dysfunction AE, certified study personnel have 24 hours to administer the NIHSS and the Modified Rankin Scale to document the presence and severity of any neurologic deficit. The NIHSS will be administered on day 1, 3, 7 (± 3), 30 (± 7), and 90 (± 7) while the Modified Rankin Scale will be administered at 30 days (± 7) and 90 days (± 7).

The NIHSS and Modified Rankin Scale are automatically generated in the EDC as event driven forms once a study coordinator has entered and saved a neurological dysfunction event on an AE CRF. Information on administering these scales can be found in Appendix II & III of the protocol.

In the event that a neurological dysfunction event occurs outside of the institution where the study participant was treated and randomized, please make every effort to obtain as much source documentation as possible, including neurological exams, NIHSS, Modified Rankin Scale, imagining exams and reports. In the event that the NIHSS and Modified Rankin Scale assessments are not administered, please note this on the CRF.

When conducting the NIHSS assessment on study participants with hearing impairment, please note that the "Best Language" category is meant to determine language capacity. Therefore, if they can

comprehend commands, repeat phrases and describe what they can see, the score for these participants should be "0" or "No aphasia".

Please use the following link as a tool when performing NIHSS on a visually impaired or a comatose study participant: http://www.healthaffairs.uci.edu/nursing/docs/stoke-conference/nih-stroke-scale.pdf.

M. *Quality of Life Assessments*

Quality of life will be measured with the Short Form 12 (SF-12) at baseline and at 90 (± 7) days post procedure. It is available in English, Spanish and French for this trial. Depression will be assessed pre-operatively and at 90 (± 7) days post procedure with the Geriatric Depression Scale (GDS). The study participant is to complete each questionnaire via self-report independently. If the study participant is unable to complete a questionnaire, the clinician, family member or friend may read the questions to the study participant and complete the questionnaire documenting the study participant's responses. There should be no coaching regarding responses. Verify that the date of administration is noted on each assessment and indicate whether it was self-administered or administered verbally by another. It is anticipated that completing these questionnaires will take the study participant 15-20 minutes.

The SF-12 and GDS (Appendix V & VI of protocol) are to be reviewed for missing or unclear data at the time of questionnaire completion. Corrections must be made with the study participant at that time. Study coordinators will enter the study participant's answers from the paper form into the EDC.

For study participants who do not complete the questionnaires, the study coordinator will enter the reason as to why the questionnaire was not completed.

N. *Barthel Index*

The Barthel Index may only be administered by a neurology trainee or a trained study coordinator preoperatively and at 30 (± 7) and 90 (± 7) days post procedure. Follow the instructions located in Appendix IV of the protocol for conducting the assessment.

O. *Confusion Assessment Method (CAM)*

At Baseline and 1, 3, and 7 (± 3) days post procedure, the 3D-CAM or CAM-ICU, as appropriate, must be administered. The 3D-CAM is the brief verbal test and the CAM-ICU should be administered to patients that are intubated. The CAM assessment should be administered by a neurology trainee or study coordinator who is trained and certified to administer the 3D-CAM and CAM-ICU. The CAM will be recorded using a digital audio recorder, uploaded through the EDC, and stored at Duke University Medical Center until the completion of study data analyses at which point the audio recordings will be destroyed. Prior to that point, the recordings will be destroyed upon receipt of a formal request for destruction from the DCC or from an enrolled patient.

Please review the CAM worksheet for research in Appendices B and C.

IX. Randomization

A representative from the DCC is available to discuss any questions regarding eligibility for randomization. DCC members are not able to randomize patients, and the DCC Information Technology team should only be contacted when technical issues prevent access to the EDC website.

Please keep the following points in mind during the randomization process:

1. Only study personnel with the task of randomization listed on the site's DOA Log are authorized to randomize study participants in this trial.
2. The EDC will prevent the user from randomizing a study participant if the minimum requirements of the Screening Registration CRF and the Randomization Eligibility CRF are not completed.
3. For the purposes of primary analysis, study participants meeting the eligibility criteria are considered enrolled in the study at the time of randomization.

Randomization Procedure

Once the *Randomization Eligibility CRF* is electronically signed by the delegated study staff member, the Randomize button will appear in the EDC allowing the study team member to randomize the study participant. **Randomization will be performed inside the operating room following sternotomy.** The timing of randomization is intended to minimize the chance of a randomized patient not undergoing investigational procedure.

When ready to randomize, please follow the steps below for randomizing a study participant:

1. Log into the Neuroprotection EDC using your unique user name and password.
2. Select the Consented Subject ready to Randomize
3. Click on the Randomize button.
4. View the *Randomization Verification CRF* to view the treatment assignment and certify the randomization of the study participant by electronically signing the *Randomization Verification CRF*.

X. Standardization of Surgical Procedure

The surgical procedures in this trial should be performed in accordance with the standard of care procedures and requirements for AVR, MVR, and CABG, and when applicable, left atrial appendage (LAA) excision or exclusion, atrial septal defect (ASD) closure or patent foramen ovale (PFO) closure. These procedures are routinely performed by either full or limited access sternotomy. This trial requires a single cross clamp for the entire time of each procedure and patients assigned to the standard cannula group should receive a standard aortic cannula of the surgeon's choice using the standard cannulation technique while those assigned to the Edwards Embol-X device or CardioGard Cannula should follow the manufacturers' IFU.

A protocol deviation must be filed, when an unplanned concomitant procedure is conducted other than those noted above and specified in the protocol. Furthermore, investigators should ensure that the index surgery operative note and other source documentation support the procedure as being unplanned.

XI. Embol-X Intra-aortic Filter

Filter sizes used pre and post cannulation will be determined by the aortic sizers (Appendix I) provided by Edwards Lifesciences and will be recorded in the EDC. Filter sizes based on the inner diameter of the aorta are detailed in Table 12 of the device IFU.

A. *Device Stocking and Re-Stocking*

An initial inventory of devices will be distributed to the sites in advance of start-up once the site has met the following regulatory requirements:

- IRB/REB approval letter
- Executed CTA
- Completed DOA Log
- A signed and dated copy of the PI's CV

Each site will receive the following initial inventory:

Product Code	Description	#
EXIS	EMBOL-X Introducer	4
EXGF24D	EMBOL-X Glide	10
EXXSD	EMBOL-X Filter, XS	4
EXSSD	EMBOL-X Filter, S	6
EXMMD	EMBOL-X Filter, M	6
EXLLD	EMBOL-X Filter, L	2
EXXLD	EMBOL-X Filter, XL	2
CA40101	Aortic Sizers, 8	3

The coordinator will complete the Embol-X device accountability log (Appendix D) for each device received and used. The coordinator will re-order a 1:1 replacement of each device used.

B. *Description of Device*

The Embol-X Intra-aortic Filter consists of three primary components:

1. A distal filter or basket assembly to capture and retain particulate emboli (positioned within the aorta). ('Filter Mesh' figure 1)
2. A locking cartridge for introduction through the side port of the Embol-X Access Device/Aortic Cannula (Appendix F) and to ensure correct orientation of the filter during use. ('Alignment Tab' figure 1)

3. A proximal syringe-like plunger mechanism to deliver and withdraw the basket into and from the aorta. The distal filter consists of a heparin-coated (Duraflo treated) mesh filter mounted on a frame. (‘Plunger Knob’ Figure 1)

Figure1. Embol-X Intra-aortic Filter

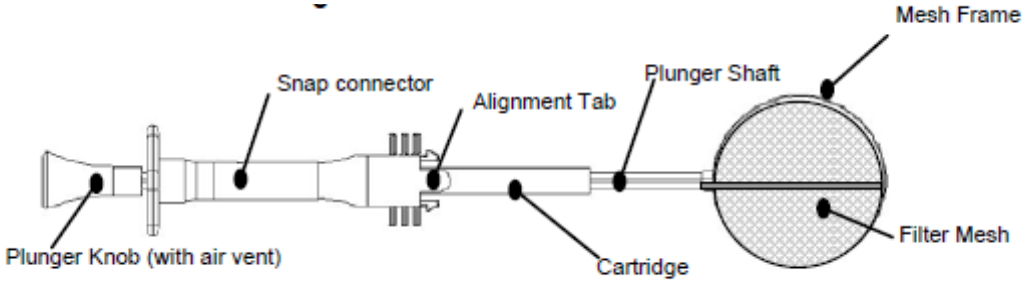


Figure2. Embol-X Intra-aortic Filter Connected with Embol-X Introducer Sheath (Appendix H)

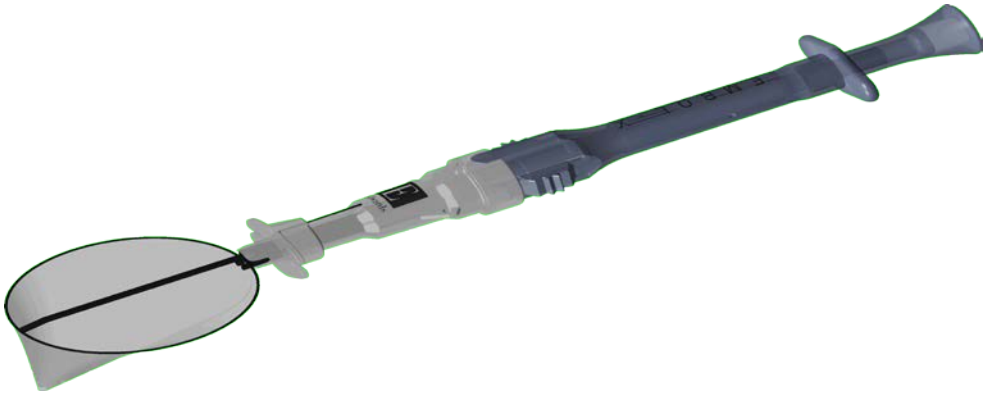
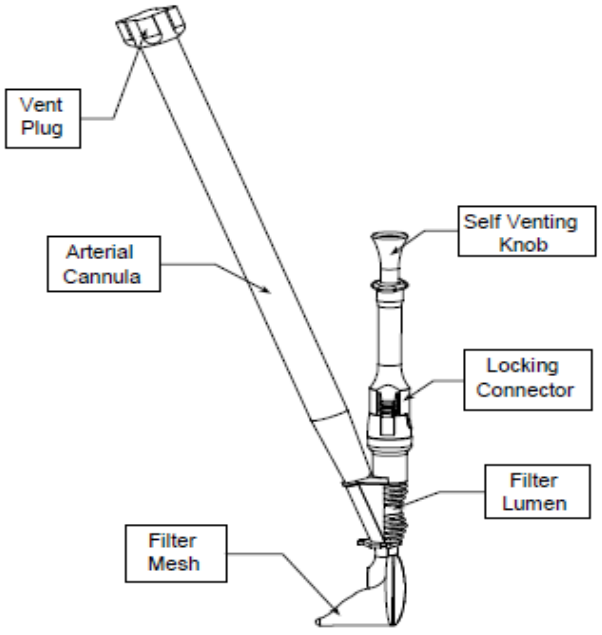


Figure3. Embol-X Intra-aortic Filter connected with Embol-X Access Device/Aortic Cannula



C. *Required Supplies for Device Use*

Sterile normal saline solution for wetting the filter prior to use

- Embol-X Access Device/Aortic Cannula for vascular access to the aorta.
- Embol-X filters (2 of each appropriate size)
- Sterilized, reusable Embol-X Aortic 'Sizers'

Please see the Embol-X filter IFU (Appendix J- US Sites) (Appendix G- Canadian Sites) for detailed instructions on device preparation before cannula insertion. Coordinators are also required to view the Edwards Embol-X device supplemental training video for visual directions on post-surgery device preparation for filter content analysis as well as the Filter Content Analysis Core Lab MOP.

Please note that filters sent to the Core Lab for analysis will not be stored at the Core Lab post analysis but will be destroyed in accordance with destruction of biohazard waste. You may contact the Core Lab or the DCC Trial Manager with any questions regarding the filter preparation process or requests for shipping materials.

XII. CardioGard Emboli Protection Cannula (Appendix K)

A. *Device Stocking and Re-Stocking*

Each site will receive the following initial inventory:

CardioGard Cannula (6)

Sorin inline arterial filters and pump tubing packs

CardioGard will provide an initial stock of devices and filter packs to the research coordinator following signoff of all initial training. This will be a minimum of six devices in addition to any used during the run-in cases at the training visit. The representative will also require a sign-off on a WI0006-3 form "US Distributor to Hospital".

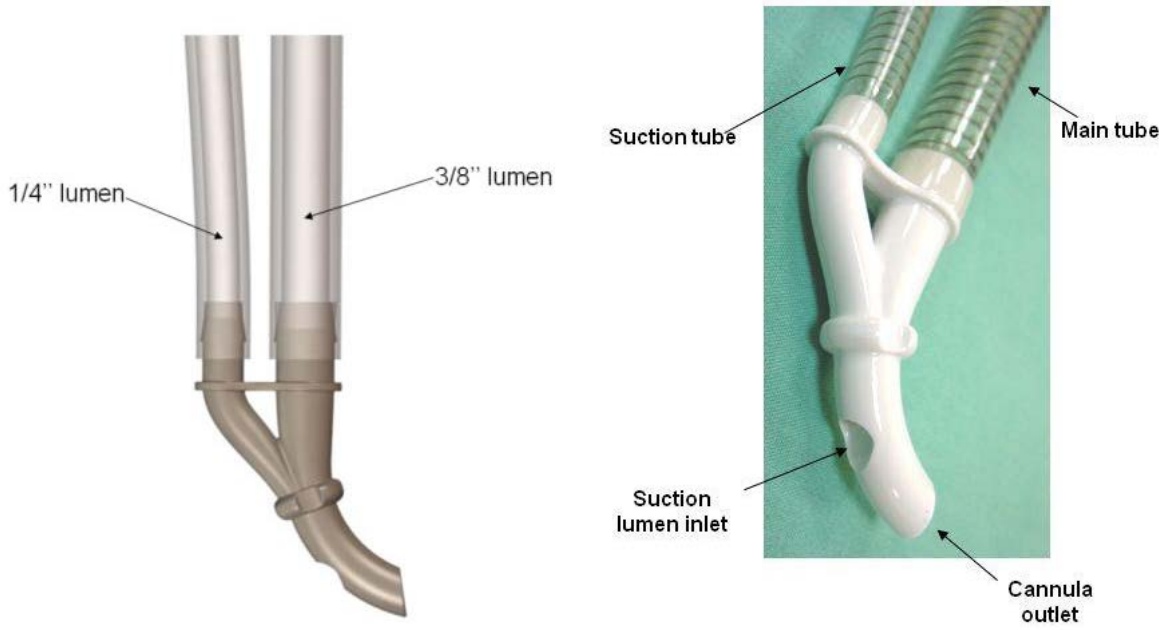
The coordinator will complete the CardioGard Cannula accountability log (Appendix D) for each device received and used. The coordinator will re-order a 1:1 replacement of each device.

B. *Device Description*

The cannula is comprised of a double lumen where the primary lumen provides oxygenated blood from the heart-lung machine to the patient and the secondary lumen performs suction of blood and embolic matter from the surgical field back to the cardiopulmonary bypass machine for filtration. The CardioGard Emboli Protection Cannula is a 24 French aortic cannula which terminates in connecter

acceptances of 3/8" (9.5 mm) and 1/4" (6.3 mm). The 3/8" channel provides the oxygenated blood from the cardiopulmonary bypass (CPB), and the 1/4" channel is used for the suction of embolic matter.

Figure4. The CardioGard Embolic Protection Cannula



Please review the device IFU for detail instructions on its use. Please also review the Filter Content Core Lab MOP for detail instructions on preparing the Sorin filter for analysis. Again, filters sent to the Core Lab for analysis will not be stored at the Core Lab post analysis but will be destroyed in accordance with destruction of biohazard waste.

The site may contact the Core Lab or the trial manager at the DCC with any questions regarding the filter preparation process or requests for shipping materials.

XIII. Hospitalization

For all hospitalizations, discharge summaries are to be uploaded directly in the EDC under the corresponding hospitalization CRF.

A. *Index Hospitalization*

The data captured on the *Index Hospitalization CRF* helps to establish the inpatient care costs and the length of stay for each study participant.

While each study participant will have their hospital admission date recorded, index hospitalization length of stay is calculated from the date and time of ICU admission following post-procedure. Any transfer between units or floors, e.g., ICU to cardiac step down unit, during the index hospitalization will also be collected with the date and time of admission and discharge recorded for each transfer.

Admission, discharge and any transfer will be recorded in chronological order on the *Index Hospitalization CRF*. For this trial, there are specific guidelines to remember when documenting the length of stay during the index hospitalization include:

- ICU is defined as all critical care floors for all departments within the hospital, including Cardiac ICU, CCU, Neurological ICU, and Medical ICU.
- Telemetry/Step down is defined as continuous telemetry monitoring not on a critical care floor.
- Regular floor is defined as any floor within the hospital that is not critical care and/or when the study participant is not monitored by continuous telemetry.

B. *Event Driven Hospitalization(s)*

Following index hospitalization discharge, all hospital readmissions will be captured using an event driven hospitalization CRF. The CRF is an event driven form located in the event driven folder of the EDC, which captures the following information:

- Date of Admission
- Reason for Hospitalization
- Number of days the study participant was in the ICU; if no days, 0 is to be entered.
- Discharge date
- Disposition at hospital discharge

Each re-hospitalization, verified as greater than 24 hours in duration, will be recorded as an individual event driven hospitalization CRF. Discharge summaries are to be uploaded directly onto the corresponding CRF. In the event a study participant is hospitalized during a study visit at another institution, the physical exam data may be taken from the outside medical record. If the study participant is hospitalized at the local institution, it is expected that the study staff conduct the assessments in the in-patient setting.

XIV. Selected Event Driven Data

AEs are collected for all randomized study participants from the time of randomization through the end of study completion. Any ongoing AE that is not resolved at the time of study completion or early termination for a study participant will be marked on the AE CRF as ‘Not resolved by completion of study’ under question 3.

Information describing the procedures for reporting AEs and unanticipated problems (UPs) and the process for reviewing and adjudicating events can be found in the CTSN Clinical & Adverse Event Reporting and Adjudication Procedures Manual.

The main purpose of this section is to provide further clarification on determining how to report AEs listed in the protocol.

As a reminder, please create a surgical procedure form for all thoracentesis procedures.

A. *Major Infection*

The definition for a major infection event is any clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated with non-prophylactic anti-microbial agents. A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The categories of infection are listed in the protocol.

The site of the infection will be entered on the *Adverse Event CRF*. Supporting source will be uploaded onto the CRF.

B. *Neurological Dysfunction*

As described in the protocol, neurological dysfunction AEs are to be identified through appropriate diagnostic testing and documented in the neurologist or other qualified treating clinician consultation note. Based on the examining physician's documentation, the event will be classified as a transient ischemic attack (TIA), stroke, toxic metabolic encephalopathy, seizure, or other.

Ischemic or Hemorrhagic Stroke

The study participant will present with focal neurologic deficit(s) that persists beyond 24 hours or less than 24 hours with image confirmation of infarction or hemorrhage.

TIA

Similar to the ischemic or hemorrhagic stroke event, the study participant will present with a neurologic deficit that will lead to further evaluation. In this case, imaging will not reveal any evidence of an infarction or hemorrhage and deficit will resolve within 24 hours of presentation.

Toxic Metabolic Encephalopathy

Disorder of the brain function that arises from abnormal systemic metabolism, infection, or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.

The laboratory values most proximal to the onset of the event for PT (seconds), PTT (seconds) and INR are to be recorded on the *Adverse Event CRF* for any of the above listed neurological dysfunction events.

C. *Mortality*

The clinical site is required to notify the DCC on the death of a randomized study participant within 24 hours of knowledge of the event. Notification is to occur electronically through the EDC using the *Mortality CRF*.

The clinical site will complete the *Mortality CRF* documenting the immediate cause of death, the primary underlying cause of death and the status of an autopsy. In addition, the investigator must provide the narrative of the events leading to the patient's death.

Sites should submit source documentation to the DCC on mortalities occurring within the enrolling site within 3 business days.

For mortalities occurring outside of the enrolling site and for which source documentation cannot be obtained promptly, sites should complete and submit to the DCC an "Initial Principal Investigator Serious Adverse Events, Unexpected Problems and Death Report" within 5 calendar days. This form can be found as an attachment to the CTSN Clinical & Adverse Event Reporting and Adjudication Procedure Document and will document the site's attempts to obtain source documentation. Sites should then continue to request the supporting source documentation, and provide the supporting source documentation to the DCC as soon as it is obtained.

The study coordinator may enter the data onto the *Mortality CRF* but source must be available to support the investigator's assessments of cause of death and the narrative. More detail on timelines for submission of source documentation to the DCC is available in the CTSN Clinical & Adverse Event Reporting and Adjudication Procedures Document.

XV. Study Completion and Investigator Statement

A. *Study Completion*

Randomization status determines the location for documenting study completion in the EDC.

Non-randomized Study Participants

Study completion will be documented using the *Randomization Eligibility CRF*. The study coordinator will select "patient will not be randomized" and enter the reason why the participant was not randomized. Data collection for these participants will conclude with the completion of the CRF. However, any existing CRFs that are incomplete are still required to be completed by the study coordinator.

Randomized Study Participants

Study completion and early termination for randomized study participants will be captured on the *Study Completion/Early Termination CRF*. Every effort should be made by the study team to have each randomized study participant complete all aspects of the study. Study coordinators are required to provide a narrative for all randomized study participants that are terminated early.

Please follow these instructions for entering the date of study completion for those study participants followed through the 90 day post-op period:

- Day 90 post-op: date entered is the date of the last data point collected for the 90 day post-op follow-up visit. (includes partial withdrawal)

Early Termination

Every effort should be made by the study team to have each enrolled study participant complete all aspects of the study. Early termination from the trial is unavoidable in some circumstances and the information provided below are guidelines for the level of detail required to document an early termination.

In addition to providing the reason for early study exit on the *Study Completion/Early Termination CRF*, study coordinators are required to provide a narrative summarizing the reason why participation was terminated early. The summary should correspond to the source documentation that establishes the reason for early termination in the study participant's record.

Please follow these instructions for entering the date of early termination:

- Mortality: date of death on the *Mortality CRF*.
- Withdrawn from the study:
    - Full withdrawal: date obtained from the source document where official study withdrawal is recorded. No data is to be collected after the date of withdrawal.
    - Partial withdrawal: end date is the last date collection of data specified in the withdrawal source documentation is obtained.
- Lost to follow-up: date of last known proof of life.

  The proof of life date will be ascertained from the date of the last patient contact or date of last patient data collected, via phone, in person or via the medical record.

Clinical sites are required to record how the last known proof of life date was determined.

For all randomized study participants that did not complete the follow-up period, the reason for early study exit will be entered. Reason for early termination should be clearly recorded in the study participant's record. The clinical site is required to document the steps taken to locate the status of a study participant and show all efforts were made to track the participant when selecting lost to follow-up as the reason for early trial exit.

Demonstration of maximum effort to establish study participant status includes:

- Record of attempts, including those to relatives, to reach the study participant via telephone, e-mail and/or mail on the Patient Contact Log;
- Documentation of undeliverable certified letter;
- Verification that no evidence exists of a service visit or encounter in the medical record;

- Confirmation that a death notice is not available through research of media sources, e.g. internet or newspaper search.

Sites may not access medical records on a patient who withdraws consent from the study without permission to do so; however, sites may review public records for information on participants who have withdrawn consent and report any information on any participant mortalities observed in a review of public records in the EDC.

Partial Withdrawal of Consent

Patients who express a desire to withdraw consent from participation should be asked if, rather than a full cessation of participation, they would modify their participation in the study to a level with which they are comfortable. Some options include telephone follow-up, allowing the site to contact the patient's treating cardiologist for records or allowing the site to continue to collect follow-up information via their medical records. The coordinator must document the patient's decision either via a signed progress note documenting a telephone conversation or via a patient's signature on a letter or other form granting permission for modified data collection. Sites must then abide by the patient's choice in the level of contact allowed from that point forward.

B. *Investigator Statement*

For all randomized study participants, the clinical site PI will electronically sign the Investigator Statement CRF to attest the accuracy and completeness of the data entered. Once the data for all randomized study participants have been monitored by the DCC and the data has been locked, access will be granted for the PI to electronically sign the Investigator Statement CRFs.

XVI. Monitoring

A. *Types of Monitoring and Trial Expectations*

Remote Monitoring using Source Document Upload

The DCC monitoring team employs a risk-based approach to remote (or centralized) monitoring. The remote monitoring of clinical trial data via the EDC system is performed with a focus on safety, study endpoints, data completion, data outliers and data integrity.

For this trial, a select group of CRFs require source documentation be uploaded directly in the EDC as listed below.

CRF Type	Upload Deadline
NP 01: Screening Registration (include redacted consent form and consent progress note)	10 business days/2 weeks

NP 02: Medical History	10 business days/2 weeks
NP 05: Laboratory Assessment	10 business days/2 weeks
NP 13: Randomization Eligibility	10 business days/2 weeks
NP 15: Index Surgical Procedure	10 business days/2 weeks
NP 03: Medications (Log)	10 business days/2 weeks
NP 19: Neurological Assessments (CAM) NP 06: Neurocognitive Testing	10 business days/2 weeks
NP 16: Epi Aortic Scan	10 business days/2 weeks
NP 17: Diffusion Weighted Imaging	10 business days/2 weeks
Event Driven Forms o Hospitalizations o Adverse Events o Surgical Procedures o Mortality	See Event Reporting and Adjudication Procedures Document

Submission of source documentation uploaded directly into the EDC will allow for as close to real time monitoring as possible of these selected CRFs to ensure that data is being captured appropriately and in a timely manner. This also allows the DCC monitors an opportunity to work with the site to identify and correct any gaps in source documentation at an early stage in the trial.

Additionally, the DCC may request source documentation from the site for CRFs in the EDC not listed above. These requests may result from changes to the protocol or trial leaderships' identification of data variables necessary for an analysis. The site should provide requested source documentation within 10 business days of each request. Redacted source documentation sent to the DCC via EDC upload must contain the Patient ID on each page.

A redacted informed consent document and a consent progress note for each patient should be uploaded to the EDC for the DCC monitors for review. The documents uploaded to the EDC should contain only the date the patient signed the form and the Patient ID on each page. This will allow the DCC monitors to review the consent process and to confirm that the correct version of the consent document was employed.

The monitor will centrally review study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event Log periodically to ensure that the site is

adhering to the study protocol and procedures. The site will forward study documents to the DCC upon request for remote monitoring.

Regulatory documentation will also be monitored remotely to ensure that site essential document binders remain current in the interim between on-site monitoring visits. The site will forward updated study documents to the DCC upon request for remote monitoring.

Remote Monitoring via access to the Site Electronic Medical Record (EMR)

Sites may provide DCC monitors with remote access to their institutional EMR systems for the purpose of remotely monitoring source documentation. If a site's institutional Informatics group allows for this remote access to be available, the site will assist DCC staff members to obtain credentialing for EMR access, provide DCC staff who are granted access with a brief tutorial of the EMR system and provide support as needed. While a majority of supporting source documentation will be included in the EMR, and therefore, will not require redacting and uploading to the EDC, certain types of source documentation will be required to be uploaded and **must be redacted and uploaded to the EDC per usual remote monitoring guidelines.** Those exceptions are as follows:

- All source documentation required for study monitoring but unavailable via the EMR system (i.e., consent forms, consent form progress notes, worksheets, patient follow-up progress notes, etc.). This may also include source documentation received from an outside hospital or from a cardiologist's office for follow-up purposes. This will vary by system; some institutions may include some or all of these documents in the EMR.
- All source documentation for any item requiring adjudication per protocol. All CTSN protocols require adjudication of AEs and mortalities. The clinical center is responsible for choosing the appropriate source documentation to represent the entirety of the event. The source documentation for all AEs and mortalities reported in the EDC must be redacted and uploaded to the appropriate CRF.

On-Site Monitoring

The DCC utilizes a risk-based approach to on-site monitoring, with a schedule that is informed by the investigational intervention, target population disease severity, phase of the trial, patient volume and site performance. The DCC will schedule an on-site visit with a site coordinator for an appropriate duration based on the assessment parameters described. A Pre-Visit letter will be sent to the site's PI and study staff. The Pre-Visit letter will include a listing of which CRFs and source will be reviewed.

Study coordinators are to have all source documents up to date and easily accessible to the monitors.

During an on-site monitoring visit, the DCC Clinical Monitor's responsibilities are to:

- Track the overall monitoring process including all data collected and entered, visit schedules, and patient screening and enrollment.

- Verify and ensure compliance with the protocol according to GCP and HIPAA (US sites only) or PIPEDA (Canadian sites only) requirements.
- Ensure that appropriate data corrections are made, dated, explained and initialed by the investigator or a representative.
- Assess the impact of any recent personnel changes on the site's ability to conduct the study.
- Verify a minimum of the following data points for all patients: date of birth, sex, signed informed consent, eligibility criteria, medical history, date of enrollment, protocol-defined serious AEs and mortalities.
- Perform review of informed consent processes and review documentation of informed consent for completeness and correctness
- Perform on-site validation checks of recorded data by reviewing source documents to determine whether the data reported in the EDC system are complete and accurate. Source documents include medical charts, initial hospital admission reports, operative procedure records and other study related notes.
- Monitor patient safety by verifying that any AE, therapy modification or concomitant medications are reported in accordance with the protocol.
- Determine whether all AEs, protocol deviations and protocol violations are appropriately reported within the required time periods according to applicable regulatory requirements as outlined in the CTSN Adverse Event Reporting and Adjudication Procedures (such as GCP, protocol definitions and IRB/REB requirements).
- Verify that any missed study visits, tests and examinations that were not performed, as well as study withdrawals and/or dropouts are explained and clearly reported as such.
- Inform the site PI about any deviations from or violations of the study protocol, MOPs, GCP and/or regulatory requirements in order for appropriate actions to be taken to prevent recurrence of the deviations and/or violations.
- Inform the investigator of any major data entry error, delays in data entry, omissions or eligibility requirement errors.
- Verify that regulatory documentation is accurate, complete, current and properly maintained.
- Verify that PI Oversight of study conduct is documented via signature or initials and date on documentation regarding eligibility, AEs and abnormal laboratory values.

The monitor may also inspect the site's facilities to verify that proper space and storage for study documents and equipment is available.

A debriefing meeting with the PI, Study Coordinator, and DCC monitor to review any notable findings will be scheduled toward the end of the on-site visit. The DCC monitor will submit a written

monitoring visit report to the DCC and NHLBI and will send a follow-up letter with findings to the PI. The report and letter will include a summary of the documentation reviewed by the monitor, any significant findings, AEs, protocol deviations and violations, missing regulatory documents and actions taken, to be taken or recommended to ensure compliance. The report and letter will include a list of Action Items. Sites are expected to complete the list of Action Items within 30 days of receipt.

Remote Monitoring Visits

The DCC will schedule remote monitoring visits with sites in a similar manner as an onsite monitoring visit in order to standardize processes and maximize efficiency, efficacy, and benefit to both the DCC monitoring effort and the sites' study staff. The DCC will schedule one to three days with a site coordinator to set aside to reconcile any open issues just as would occur during a traditional onsite monitoring visit. A Pre-Visit letter will be sent to the site's PI and study staff just as a Pre-Visit letter is sent prior to an onsite monitoring visit. The Pre-Visit letter will include a listing of which CRFs and source will be reviewed. During the remote monitoring visit, the monitor will interact via telephone, email, and EDC with the site study staff to perform source verification. A debriefing phone-call will be arranged between the PI, Study Coordinator, and DCC monitor to review any notable findings, just as the in-person debriefing meeting is held during an onsite monitoring visit. At the conclusion of the remote visit, a monitoring report will be generated by the DCC monitor and sent to the NHLBI, and a Post-Visit letter sent to the site, just as is traditionally sent after an onsite monitoring visit.

Both the DCC monitoring team and the site study staff will be expected to continue to interact via the CTSN EDC on a rolling basis, however scheduling remote monitoring visits will establish a period of time when query resolution and source verification is expected to be reconciled. Formalizing a review period will give both parties a shared deadline and the opportunity for better time management and resource allocation.

B. *Source documentation requirements*

It is highly recommended that study coordinators use the case report forms and schedule of assessments in the protocol to develop a plan for identifying and standardizing where source documentation for data verification will be collected across all study participants at their clinical center. As part of study startup and prior to first enrollment, clinical sites are encouraged to conduct a gap analysis to identify any data points that are not routinely documented in the medical record.

The medical record is the gold standard for source documentation as it includes clinic notes, lab reports, pharmacy orders and dispensing records, admission/discharge notes, test results and so forth. However, the DCC understands that there may be data points required for this trial that are not collected as routine practice at a clinical site in the medical record for this patient population. Clinical sites may create source documents for the purposes of collecting source data that are not included in the medical record. **It is important to remember that "source" documentation is where the information is first recorded.**

Source documentation best practices include ensuring that any document is attributable, legible, contemporaneous, original, and accurate (ALCOA; see http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf). Any source document that is not part of the medical record must be signed and dated by the study team member gathering the source data. Additionally, all hand-written source documentation must be initialed and dated on each page by the document's author with a full signature and date on the last page of a source document. Any corrections made on source documents need to be crossed out with a single line, signed and dated.

When using a CRF as source documentation please ensure that you are using the most up to date version of the CRF as CRFs are updated periodically.

In order to document investigator oversight of the study, the PI (or a designated MD sub-investigator) should sign and date laboratory reports, ECGs and other source documentation with a note of any clinically significant findings, if applicable.

For lab values with whole number values, any values of 0.5 or higher should be rounded to the next whole number. Values less than or equal to 0.4 should be rounded down to the lower whole number.

In preparation for upcoming study visits, study coordinators should review patient records for previously undocumented AEs, procedures and hospitalizations.

The clinical site must ensure that all patient source documentation is complete, orderly and stored in a secure location. For electronic records, the site should abide by institutional policies for the storage of private health information (PHI). For paper records containing any PHI, sites must ensure that the files are double-locked, that is, in a locked filing cabinet within a locked office or suite.

C. *Informed Consent Documentation*

Review each informed consent document prior to initiating the consent process to be sure the correct version is being employed. During the informed consent process, be sure that each space for initials, signature and date is complete. If deficiencies are identified after the informed consent process, document them in a progress note or note to file. Ensure that appropriate signatures, initials or dates are obtained at the next available opportunity.

Be sure that each patient needing to be re-consented (because of a newly approved version of the informed consent document) is approached at the next available opportunity.

Ensure that your documentation of the consent process in a progress note contains at least the following components:

- the patient was deemed to meet study eligibility requirements
- the patient was given the opportunity to ask questions and the questions were answered
- documentation of any family members or witnesses who participated in the consent process
- the patient understands the study follow-up requirements and study procedures

- a copy of the consent form was provided to subject.
- all study procedures occurred after the ICF was signed.
- the study is optional and that the patient was informed of alternative procedures.

D. *Queries*

DCC monitors will provide feedback as they source verify data points via the EDC query system. Sites should review their EDC homepage for new queries regularly and respond to queries as soon as possible. The EDC will track the timeliness of query responses.

E. *Data Completion Reports*

Although study enrollment is often viewed as the measure of a site's success, patient retention and data completeness are the deliverables required for each patient enrolled. Failure to capture study endpoints for each patient compromises the overall data set. The DCC will generate a monthly Data Completion Report to inform the clinical sites of outstanding data and to provide information on site performance. Site PIs should review each Data Completion Report to stay abreast of site performance and to be aware of any missing primary or secondary endpoint data. The DCC will track performance over time and will schedule a teleconference with the site PI if data completeness rates fall below a certain level or do not improve after discussion with the study coordinator.

XVII. Study Closeout

Once the study has been completed and all data and finalized CRFs are submitted by the site, the DCC and the site will work together to ensure that all study files are completed and ready for close-out. Study closeout tasks to be completed by the clinical site include:

- Submission of a request for study closure to the IRB/REB
- Submission of IRB/REB acknowledgement of study closure to the DCC
- Adding end dates and obtaining the PI signature on the DOA Log and submitting final DOA Log to the DCC
- Providing the DCC with the institutional policy on record retention for your clinical center
- Providing the DCC with documentation of the location of study records' storage
- Completing any outstanding tasks outlined by the DCC

Once a site has completed the tasks and all data has been monitored and locked, the PI will sign an attestation statement confirming the accuracy and completeness of the data collected for all study participants and verifying that the regulatory documents submitted are accurate and complete.

APPENDIX A: CTSN DCC Trial Roster and Contact Information

Screening, Enrollment and General Trial Questions:

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- To be used for regulatory document submissions

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EDC Tech Support:

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APPENDIX B: 3D-CAM Worksheet for Research

3D-CAM Instrument

For Research

Evaluator:

Date:

Patient:

Time:

COGNITIVE FUNCTION

Now I'd like to ask you some questions to check your memory. Don't worry if you don't know the answers.

[YOU MAY REPEAT EACH QUESTION ONCE]

(WRITE PATIENT'S ANSWERS TO ALL QUESTIONS AND CIRCLE NUMBER AS INDICATED)

ORIENTATION	CORRECT	ERROR	REF	DK/No Response
1. **What is the year?**	1	2	7	8
2. **What is the day of the week?**	1	2	7	8
3. **What type of place is this?**	1	2	7	8

If any of 3 items above are anything other than correct, feature 3 is present

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DIGIT SPAN

[SAY DIGITS AT RATE OF ONE PER SECOND]

Now I am going to read some numbers, but I want you to repeat them in backwards order from the way I read them to you. So for example if I said 6-4, you would say 4-6.

DIGITS BACKWARD		Response	Correct	Error	REF	DK/No Response
4.	**7 - 5- 1**	___ - ___ - ___	1	2	7	8
5.	**8 - 2 - 4 - 3**	___ - ___ - ___ - ___	1	2	7	8

6. DAYS OF WEEK BACKWARDS

Can you tell me the days of the week backwards? Say Saturday as your first day.

(May prompt with: "what is the day before Saturday? or if subject stops with Day X, say " what is the day before day X? …." This prompt may be used 2 times in total. If participant starts reciting days forward repeat overall instructions.

Day	Response	Correct	Error	REF	DK/No Response
Saturday	_____	1	2	7	8
Friday	_____	1	2	7	8
Thursday	_____	1	2	7	8
Wednesday	_____	1	2	7	8
Tuesday	_____	1	2	7	8
Monday	_____	1	2	7	8
Sunday	_____	1	2	7	8

Record response verbatim

Coding Instructions: If the subject leaves 1 day out, total recorded = 6, if 2 days are reversed, total recorded =5

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7. MONTHS OF YEAR BACKWARDS

Can you tell me the months of the year backwards? Say December as your first month?

(May prompt with: "what is the month before December? or if the subject stops with Month X, " say what is the month before Month X? ...." This prompt may be used 2 times in total. If participant starts reciting months forward repeat overall instructions)

Month	Response	Correct	Error	REF	DK/No Response
December	_____	1	2	7	8
November	_____	1	2	7	8
October	_____	1	2	7	8
September	_____	1	2	7	8
August	_____	1	2	7	8
July	_____	1	2	7	8
June	_____	1	2	7	8
May	_____	1	2	7	8
April	_____	1	2	7	8
March	_____	1	2	7	8
February	_____	1	2	7	8
January	_____	1	2	7	8

Record response verbatim.

Coding Instructions: If the subject leaves one month out, total recorded = 11, if the months are reversed, total recorded = 10

*****If any of items 4, 5, 6, or 7 above are anything other than correct, feature 2 is present***

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PATIENT-REPORTED SYMPTOMS:
If the respondent answers yes to any of the following questions, probe him/her for more details and note responses. E.g. Frequency

If the respondent's answers are nonsensical, code as 8.

Now I am going to ask you some questions about how you have been thinking during the past day.

8. **Have you felt confused at any time during the past day?**

   1 - No 2 - Yes 7 - REF 8 – DK/Uncertain/NR 9 – NA

9. **During the past day did you think that you were not really here [in the hospital]?**

   1 - No 2 - Yes 7 - REF 8 – DK/Uncertain/NR 9 – NA

10. **During the past day, did you see things that were not really there?** (If patient is blind skip and code 9)

    1 - No 2 - Yes 7 - REF 8 -DK/Uncertain/NR 9 – NA

If any of items 8, 9, or 10 above are anything other than 'no', feature 1 is present

End of Patient Interview

Thank you so much for your time.

Proceed to area for completion of interview observation items and final coding.

Used with permission. The SAGES Study: Training Manual and Questionnaires; 2010; Boston, Aging Brain Center.

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INTERVIEWER OBSERVATIONS	
11. Was the patient sleepy, stuporous, or comatose during the interview?	FEATURE 4 IS PRESENT? 1 – No 2 - Yes
12. Did the patient show hypervigilance such as excessively strong responses to ordinary objects/stimuli in the environment, for example, being inappropriately startled, etc? Note: Triggers altered level of consciousness	FEATURE 4 IS PRESENT? 1 – No 2 - Yes
13. Was the patient's Flow of ideas unclear or illogical, for example saying something non-sensical, unrelated to the interview (tangential) or making contradictory statements	FEATURE 3 IS PRESENT? 1 – No 2 - Yes
14. Conversation rambling, for example did he/she give inappropriately verbose and off target responses?	FEATURE 3 IS PRESENT? 1 – No 2 - Yes
15. Was the patient's speech unusually limited or sparse? (e.g. yes/no answers) or unusally slow or halting?	FEATURE 3 IS PRESENT? 1 – No 2 - Yes
16. Did the patient have trouble keeping track of what was being said during the interview, for example, fail to follow instructions or answer questions one at a time?	FEATURE 2 IS PRESENT? 1 – No 2 - Yes
17. Did the patient fail to attend to the interview due to being inappropriately distracted by environmental stimuli, for example, respond to questions asked of roommate?	FEATURE 2 IS PRESENT? 1 – No 2 - Yes
18. Did the patient's level of consciousness fluctuate during the interview, for example, start to respond appropriately and then drift off?	FEATURE 1 IS PRESENT? 1 – No 2 - Yes
19. Did the patient's level of attention fluctuate during the interview, e.g., did the patient's focus on the interview or performance on the attention tasks (digit span, days & months backwards) vary significantly?	FEATURE 1 IS PRESENT? 1 – No 2 - Yes
20. Did the patient's speech/thinking fluctuate during the interview, for example, patient spoke slowly for a while, then sped up?	FEATURE 1 IS PRESENT? 1 – No 2 - Yes

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APPENDIX C: CAM-ICU Worksheet for Research

CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if Present
Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes ☐	☐
Feature 2: Inattention		
Letters Attention Test (See training manual for alternate **Pictures**) Directions: Say to the patient, *"I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand."* Read letters from the following letter list in a normal tone 3 seconds apart. **S A V E A H A A R T** or **C A S A B L A N C A** or **A B A D B A D A A Y** **Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."**	Number of Errors >2 ☐	☐
Feature 3: Altered Level of Consciousness		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero ☐	☐
Feature 4:Disorganized Thinking		
Yes/No Questions (See training manual for alternate set of questions) 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? **Errors are counted when the patient incorrectly answers a question.** **Command** Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2nd part of command ask patient to "Add one more finger" **An error is counted if patient is unable to complete the entire command.**	Combined number of errors >1☐	☐

Overall CAM-ICU		
Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive	Criteria Met ☐	☐ CAM-ICU Positive (Delirium Present)
	Criteria Not Met ☐	☐ CAM-ICU Negative (No Delirium)

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APPENDIX D: Device Accountability Logs

NEUROPROTECTION TRIAL CARDIOGARD DEVICE ACCOUNTABILITY LOG

Site Name:_____ Site Number:_____ Principal Investigator: _____

Date Received	Lot Number	Used By Date	Name of Person Entering Data	Date Removed From Inventory	Product Returned to Manufacturer?	Procedure Date	Subject ID	Comments	Name of Person Entering Data

NEUROPROTECTION TRIAL CARDIOGARD DEVICE ACCOUNTABILITY LOG

Site Name:_____ Site Number:_____ Principal Investigator: _____

Date Received	Lot Number	Used By Date	Name of Person Entering Data	Date Removed From Inventory	Product Returned to Manufacturer?	Procedure Date	Subject ID	Comments	Name of Person Entering Data

NEUROPROTECTION TRIAL EDWARDS EMBOL-X DEVICE ACCOUNTABILITY LOG

Site Name:_____ Site Number:_____ Principal Investigator: _____

Date Received	Lot Number	Used By Date	Name of Person Entering Data	Date Removed From Inventory	Product Returned to Manufacturer?	Procedure Date	Subject ID	Comments	Name of Person Entering Data

NEUROPROTECTION TRIAL EDWARDS EMBOL-X DEVICE ACCOUNTABILITY LOG

Site Name:_____ Site Number:_____ Principal Investigator: _____

Date Received	Lot Number	Used By Date	Name of Person Entering Data	Date Removed From Inventory	Product Returned to Manufacturer?	Procedure Date	Subject ID	Comments	Name of Person Entering Data

APPENDIX E: Device Training Attestation Form(Embol-X & CardioGard Device)

NEUROPROTECTION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT

Device Overview and Use/Handling

Site Name: _____

Device Name: _____

I was present for training on ____/_____/201_ which included a detailed review of the device handling and use according to the "Instructions For Use" (IFU). I agree to comply with the Directions for Use and guidelines presented.

Site Trainees:

Print Name	Title	Signature

Training Personnel:

I trained the above personnel on _____/_____/201_ on device handling and use, and specifically on opening the device packaging in the OR according to the IFU. All personnel are experienced and qualified employees of the hospital.

Print Name	Title	Signature

CONFIDENTIAL

APPENDIX F: Embol-X Access Device/Aortic Cannula Instructions for Use

Edwards Lifesciences

English

INSTRUCTIONS FOR USE
EMBOL-X ACCESS DEVICE / AORTIC CANNULA

Caution: Federal law (U.S.A.) restricts this device to sale by, or on the order of, a physician.

DESCRIPTION

The EMBOL-X access device/aortic cannula is designed to provide arterial return of oxygenated blood from the cardiopulmonary bypass (CPB) circuit. The EMBOL-X access device/aortic cannula consists of two components, the introducer port component and the aortic cannula component. The EMBOL-X access device/aortic cannula component consists of a standard ¾" ID wire reinforced tube body having a curved tip end and a flange or suture bump for suture attachment. Attached to the side of the tip end is an introducer port having a single lumen housing and a removable self-venting keyed snap-lock obturator. The attached introducer port acts as an intravascular hemostasis conduit that can accommodate the introduction of the EMBOL-X Intra-aortic Filter. When the obturator is removed insertion of the Filter is necessary. The EMBOL-X access device/aortic cannula is 24 FR (8.0 mm) at its distal tip. Models include a J tip and an auto dilating tip. The device is packaged sterile and non-pyrogenic, is single use only, and comes with a separate optional use vent plug and T-connector/vent cap combination for cannula venting. The EMBOL-X access device/aortic cannula shall be hereafter referred to as the EMBOL-X "Access Device."

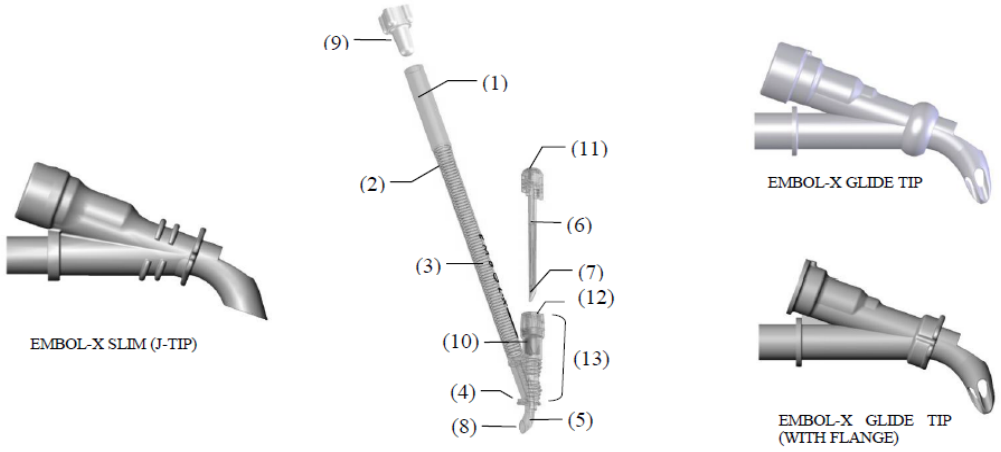

Figure 1. The EMBOL-X access device/Aortic Cannula.

DEVICE DESIGN FEATURES

The EMBOL-X access device has a clear cannula body (1) for blood visualization with a standard sized ¾" ID tube for common connectors. The PVC body (2) is wire-reinforced for flexibility and strength. Orientation marks on cannula body (3) are provided to identify the tip orientation and flow direction. An integrated tip end flange or suture bump (4) is provided for cannula stability and for suture attachment once inserted. A grooved cannula tip (5) allows the introduction of the Intra-aortic Filter through the attached Introducer port (13) without the need of an additional puncture site. An obturator (6) is provided to prevent the Introducer port from back bleeding when being used. A matched tapered obturator tip configuration (7) to cannula tip groove (5) allows for a smooth unobstructed puncture site entry. A curved 24 FR plastic tip is provided (8). A separate optional use cannula vent plug (9) is provided for cannula air venting without fluid leakage. An internal one-way Introducer port valve (10) helps to minimize back bleeding when an intravascular device or if the obturator is not in place. The obturator contains an integrated self-venting plug (11) feature to vent air via a through hole channel in its shaft. The Introducer port housing contains a keyed snap-lock (12) to orient the obturator tapered tip and retain it in place.

INDICATIONS FOR USE

The EMBOL-X access device is indicated for the perfusion of the ascending aorta during short-term (≤ 6 hours) cardiopulmonary bypass (CPB) surgery where procedures may require the hemostatic introduction and removal of compatible intravascular devices into the vascular system.

CONTENTS

The EMBOL-X access device is individually packaged with a cannula vent plug, a T-connector/vent cap combination and an Introducer port obturator.

HOW SUPPLIED

The EMBOL-X access device is provided STERILE and NON-PYROGENIC when in an unopened, undamaged packaging and is sterilized by ethylene oxide. Do not use if device shows signs of damage (i.e., cuts, kinks, crushed areas), or if package is damaged or open.

STORAGE AND HANDLING

Store in a cool, dry, dark place until ready for use. DO NOT expose to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids.

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CONTRAINDICATION

- Aortic trauma
- Aneurysm of the ascending aorta

WARNINGS

- DO NOT use the device if any of the components show signs of leakage or damage.
- This device is designed, intended, and distributed for single use only. **Do not re-sterilize or reuse this device**. There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- During cannulation, extreme caution should be exercised if there is a possibility of aorta tissue dissection.
- Avoid pointing the cannula tip directly toward the aortic arch branch arteries to minimize the possibility of directing any dislodged emboli into the arteries.
- Position the EMBOL-X access device AT LEAST 1.5 cm away from the ostium of the bracheocephalic artery (i.e. towards the aortic valve) to reduce the risk of damaging the bracheocephalic ostium or obstructing bracheocephalic blood flow.
- To assure proper Filter introduction using the Introducer port, the cannula component of the EMBOL-X access device must be positioned so that the Introducer port is perpendicular to the vessel. The tip end flange or suture bump must also be fully abutted against the vessel.
- Position the aortic cross clamp AT LEAST 2.0 cm away from the Access Device. Failure to do so may result in difficulty with insertion and removal of the Filter from the Introduction port.
- Keep the vent plug dry prior to use. The porous vent plug is designed to vent air when dry and may not function as intended if wet.
- If pressures exceed acceptable clinical limits, check the position of the device tip and/or cannula patency
- The base of the cannula component must be held to prevent excess movement when manipulating the cannula or when using the Introducer port. Failure to do so may cause injury to the aorta.
- If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X Access Device/Aortic Cannula can be removed. The EMBOL-X Access Device/Aortic Cannula can be removed with the EMBOL-X filter inserted using standard techniques.
- Do not manipulate the EMBOL-X access device while the Filter is deployed through the Introduction port. If the cannula component must be manipulated, first retract the Filter. Failure to do so may cause injury to the aorta.
- The EMBOL-X access device and the EMBOL-X Filter should only be used in an operating room completely equipped for conventional cardiac surgery and by a surgeon trained in cardiac surgery.
- DO NOT expose the device to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids. The housing may weaken or crack and subsequent use may result in patient injury.
- Anticoagulation should be routinely monitored during all CPB procedures.
- Secure the connector to cannula junction prior to initiating bypass.
- Wire-reinforced cannulae should be clamped in the non-reinforced section located at the connector end since clamping of the reinforced section may produce permanent cannula deformation, thereby impeding flow through the cannula and risking puncture or tearing of the cannula.

PRECAUTIONS

- DO NOT use device if the package sterile integrity appears jeopardized or is opened or damaged.
- Exercise care during the connection of the cannula component and the CPB circuit to ensure that no air is trapped in the perfusion line.
- Placement, location, and orientation of the sutures in the vessel are critical to proper positioning of the cannula component. Once the Access Device is secured with the sutures, it is difficult to change the position of the aortic cannula.
- When using the Introducer port, always refer to the filter's Instructions for Use for any specific instructions, precautions, or warnings prior to its use.
- DO NOT exceed the maximum recommended flow.
- Proper surgical procedures and techniques are the responsibility of the medical profession. Described procedures are provided for informational purposes only. Each physician must determine the appropriate use of this device for each patient based on medical training, experience, the type of procedure employed, and the benefits and risks associated with device use.
- Dispose of used product in accordance with established hospital protocols for biohazards.

COMPLICATIONS

Possible adverse effects include, but are not limited to, the following:

- Arterial thrombosis
- Plaque embolization
- Air embolism
- Excessive blood loss
- Wound infection
- Sepsis
- Vascular dissection or perforation

INSTRUCTIONS FOR USE

I. Inspection Prior to Use

- Visually examine the following:
  - The package integrity. If the package sterile integrity appears to have been jeopardized, DO NOT USE.
  - Verify that the EMBOL-X access device has not been damaged or has components missing. If the device appears damaged or has components missing, DO NOT USE.
  - The cannula vent plug and the obturator's built in self-venting plug for exposures to any fluids. This would prevent the plugs from venting air properly. The plugs are only able to vent air once and will stop venting once fluids contact it.

II. Preparation for Use

- Carefully insert the obturator into the Introducer port and verify that the obturator's snap-lock connector snaps into place. Inspect the obturator in the Introducer port lumen for a smooth transition and verify easy removal by squeezing the obturator locking tabs and pulling the obturator out of the Introducer port lumen. Carefully re-insert the obturator back in.
- Just prior to access device/aortic cannulation, insert the supplied cannula vent plug or T-connector/vent cap combination into the proximal end of the cannula tube. Moisten the aortic cannula tip component by submerging it in sterile saline. Take care not to expose the cannula vent plug or vent cap or the obturator top's self-venting plug to any fluids. Exposure to fluids prior to use will prevent the plug from venting air properly. The vent plugs can only vent air once before fluids contact it.
- The Introducer port can also be vented manually if the obturator's self-venting plug has been inadvertently exposed to fluids.

III. Insertion of the EMBOL-X access device

- Locate the desired cannulation site on the ascending aorta.
- Using the appropriate surgical technique, place purse string sutures at the desired cannulation site. To insure the cannula component will be firmly attached, use double purse string sutures.
- Remove any loose tissue from the center of the purse string sutures site.
- After ensuring that adequate system heparinization has been obtained, make an incision in the aorta within the purse string suture site using an appropriate surgical blade.
- Place a finger over the incision to control bleeding.

WARNING: During cannulation with the EMBOL-X access device extreme caution should be exercised if there is a possibility of aorta tissue dissection.

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- With a slight "hooking" motion, insert the cannula tip in through the incision site placing the curved tip away from the aortic valve.
- Assure penetration of the cannula tip into the aorta by observing that the cannula component fills with blood. The cannula vent plug or cap will prevent back bleeding during cannula component insertion.

WARNING: Avoid pointing the cannula tip directly toward the aortic arch branch arteries to minimize the possibility of directing any dislodged emboli into the arteries.

WARNING: To reduce the risk of damaging the bracheocephalic ostium or obstructing bracheocephalic blood flow, position the EMBOL-X access device AT LEAST 1.5 cm away from the ostium of the bracheocephalic artery (i.e. towards the aortic valve).

WARNING: To assure proper device introduction when using the Introducer port the cannula component must be positioned so that the Introducer port is perpendicular to the vessel. The tip end flange or suture bump must also be fully abutted against the vessel.

- **WARNING:** Cannulae with a curved tip will have a printed orientation line on the cannula body; do not use if line is missing or illegible. Orient the curved tip so the flow is directed superiorly, away from the aortic valve.
- Rotate and orient the curved tip so that arterial return flow is directed distally, away from the aortic valve and heart. On the cannula component, the orientation mark is located OPPOSITE to the tip flow direction. The orientation mark should be situated such that it is facing TOWARDS the direction of the aortic valve or heart.
- Tighten the purse string sutures to stabilize the Introducer, ensuring that they are positioned in the cutouts on the flange.
- The air in the Introducer port lumen must also be purged. After the cannula component is secured, the Introduction port may be de-aired by removing the obturator slowly, observing the blood leaking around the obturator, replacing the obturator, and verifying that it locks in place. See the section on "*Using the Introducer port of the EMBOL-X access device/Aortic Cannula*".

WARNING: The base of the cannula component must be held to prevent excess movement when manipulating the cannula or when using the Introducer port. Failure to do so may cause injury to the vessel.

WARNING: Position the aortic cross clamp AT LEAST 2.0 cm away from the EMBOL-X access device. Failure to do so may result in difficulty with insertion and removal of devices from the Introduction port.

- Clamp the aortic cannula body and remove the cannula vent plug or vent cap from the cannula.
- Connect the cannula component to the arterial line of the extracorporeal CPB circuit.
- Remove all clamps from the cannula and lines prior to initiating cardiopulmonary bypass. Purge any remaining air in the aortic cannula and CPB circuit system.
- Initiate cardiopulmonary bypass. Refer to Figure 2 for information on pressure drops across the EMBOL-X access devices.

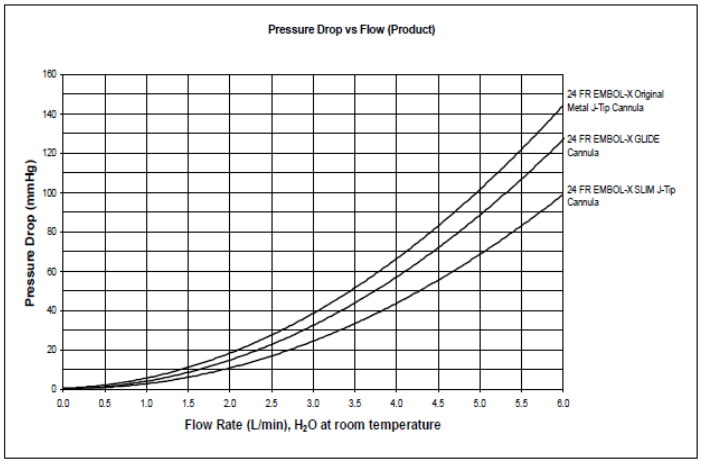

Figure 2. Pressure drop across the EMBOL-X access device/Aortic Cannula. Data represents in vitro testing using H_2O at room temperature. Actual clinical results may differ.

EMBOL-X access device Removal

- Reduce the arterial flow rate until the patient is able to be completely weaned from cardiopulmonary bypass.
- Once the patient is stabilized, proceed with EMBOL-X access device removal by loosening the sutures and removing the cannula component from the vessel while simultaneously pulling the sutures tightly to achieve hemostasis.

IV. Using the Introducer Port of the EMBOL-X access device/Aortic Cannula

- Prior to inserting the Filter into the Introducer port, refer to the specific EMBOL-X Filter device Instructions for Use for any specific instructions, precautions, or warnings.

WARNING: Hold the base of the cannula component to prevent excess movement while removing or re-inserting the obturator or the Filter through the Introducer port. Failure to do so may cause injury to the vessel.

- The air in the Introducer port lumen must be purged prior to its use. To achieve this, partially retract the obturator to vent the Introducer port lumen via the obturator shaft's vent groove. Continue to retract the obturator until complete air venting has been achieved. Check for blood visibly coming out of the valve to indicate air venting is complete and that there is proper penetration of the aortic cannula component into the vessel. Carefully re-insert the obturator and lock in place.
- To introduce the Filter through the Introducer port, hold the base of the cannula component, unlock the obturator and remove it from the Introducer. The one-way valve will prevent excessive back bleeding. Save the obturator for later use.
- Holding the base of the cannula component to prevent excessive manipulation force on the vessel, slowly insert the Filter into the Introducer. Follow the instructions for using EMBOL-X Intra-aortic Filter.
- If excessive back bleeding occurs with the Intra-aortic Filter in place, remove and reinsert a new Filter.

WARNING: Do not manipulate the cannula component while a device is deployed through the Introduction port. If the cannula component must be manipulated, first retract the Filter. Failure to do so may cause injury to the aorta.

Device Retraction and Removal

- Hold the base of the cannula component to stabilize the device and prevent excessive force on the vessel.
- While holding onto the base of the cannula component, gently withdraw the Filter. Refer to the specific Instructions for Use for, precautions, or warnings when using the Intra-aortic Filter .
- Upon device removal, place the obturator back into the Introducer and lock into place.

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WARNING: If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X Access Device/Aortic Cannula can be removed. The EMBOL-X Access Device/Aortic Cannula can be removed with the EMBOL-X filter inserted using standard techniques.

DISCLAIMER OF WARRANTY

EDWARDS LIFESCIENCES MAKES NO EXPRESS OR IMPLIED WARRANTY WITH RESPECT TO THE PRODUCT(S) SOLD HEREUNDER, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, WHICH WARRANTIES ARE EXPRESSELY DISCLAIMED. TO THE EXTENT THAT ANY PRODUCT DESCRIPTIONS AND/OR SPECIFICATIONS ARE SET FORTH HEREIN, SAID SPECIFICATIONS AND/OR DESCRIPTIONS ARE INTENDED ONLY AS GENERAL LANGUAGE AND DO NOT CONSTITUTE AN EXPRESS WARRANTY THAT THE PRODUCT SHALL CONFORM TO THE DESCRIPTION AND/OR SPECIFICATION OF THE PRODUCT.

For product information or questions pertaining to sales and service, please contact the representative in your area or Edwards Lifesciences LLC directly.

United States/Canada

Edwards Lifesciences LLC
Irvine, CA 92614-5686

ID	LOT			Caution		STERILE EO		#		Rx Only	REF
Inner Diameter	Lot Number	Consult Instructions for Use	Use By Date		Non-Pyrogenic	Sterilized using Ethylene Oxide	Single Use Only	Quantity	Do not use if package is damaged	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician	Catalogue Number

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APPENDIX G: Embol-X System Instructions for Use (for Canadian Sites Only)

Edwards Lifesciences

EMBOL-X SYSTEMS

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ENGLISH

INSTRUCTIONS FOR USE
THE EDWARDS EMBOL-X PROTECTION SYSTEM

Not for sale in the USA

See Figures at the end of the Instructions for Use.

DESCRIPTION

The EMBOL-X system is comprised of either:

1. The EMBOL-X access device / aortic cannula (hereafter referred to as the EMBOL-X access device) and the EMBOL-X intra-aortic filter, OR
2. The EMBOL-X introducer sheath and the EMBOL-X intra-aortic filter (see the EMBOL-X introducer sheath Instructions for Use).

The EMBOL-X system with the EMBOL-X access device is designed to provide arterial return of oxygenated blood from the cardiopulmonary bypass (CPB) circuit and to filter microemboli greater than 150 microns in diameter. It consists of a two-lumen arterial cannula and an intra-aortic filter which is inserted into the ascending aorta during procedures that utilize CPB. The first cannula lumen permits inflow of arterial blood from the CPB circuit into the ascending aorta and the second cannula lumen is for filter insertion.

The EMBOL-X system with the EMBOL-X introducer sheath is designed to filter microemboli greater than 150 microns in diameter. It consists of a one-lumen introducer sheath and an intra-aortic filter which is inserted into the ascending aorta during procedures requiring the use of the EMBOL-X intra-aortic filter. The lumen is designed for filter insertion.

The EMBOL-X access device is 24 FR (8 mm) at its distal tip, with an effective flow diameter of 22 FR (7.3 mm). The proximal end connects with standard perfusion tubing (3/8 inch [9.5-mm] diameter) that is used in CPB circuits. A locking obturator is packaged with the cannula to occlude the filter lumen during insertion of the EMBOL-X access device and when the filter is not in place. The filter lumen has a one-way valve that is designed to minimize backbleeding when inserting and removing the filter.

The EMBOL-X intra-aortic filter, which is provided in a cartridge that locks into the filter lumen, is inserted through the lumen by depressing a syringe-like plunger mechanism. The self-venting knob allows the air in the cartridge to automatically vent when the cartridge is inserted into the cannula/introducer sheath. The filter is withdrawn by pulling up on the plunger. On insertion, the filter opens to fill the diameter of the ascending aorta. The filter is intended to be inserted temporarily at any time during surgical procedures requiring CPB (EMBOL-X access device / EMBOL-X introducer sheath) or during other cardiac surgical procedures (EMBOL-X introducer sheath). Each filter can be used for a maximum of 60 minutes. The EMBOL-X intra-aortic filter is heparin coated (Duraflo treatment) to prevent formation of thrombus on the filter during use. The EMBOL-X intra-aortic filter is available in several sizes to accommodate aortas of varying diameters up to a maximum of 40 mm.

INTENDED USE / INDICATIONS FOR USE

The EMBOL-X System combines the functions of standard arterial cannula with an added filtration mechanism to capture debris that may result from cardiac surgery. The EMBOL-X access device /aortic cannula is intended for perfusion of the ascending aorta during surgical procedures that require CPB. The EMBOL-X intra-aortic filter is intended for the removal of particulate emboli during surgical procedures.

CONTRAINDICATIONS FOR USE

- Aneurysm of the ascending aorta
- Aortic trauma
- Porcelain aorta
- Devices with a Duraflo coating are contraindicated in patients with a known sensitivity to heparin.

WARNINGS

- Keep the vent plug dry prior to use. The porous vent plug is designed to vent air when dry and may not function as intended if wet.
- If pressures exceed acceptable clinical limits, check the position of the device tip and/or cannula patency.
- During cardiopulmonary bypass, ensure proper levels of anticoagulant therapy are maintained.
- The cannula is intended for short-term use only (<6 hours)
- Securely tie-band the connector to cannula junction prior to initiating bypass.
- Wire-reinforced cannulae should be clamped in the non-reinforced section located at the connector end since clamping of the reinforced section may produce permanent cannula deformation, thereby impeding flow through the cannula and risking puncture or tearing of the cannula.
- Use extreme caution when inserting the EMBOL-X access device if there is a possibility of tissue dissection of the aorta.
- Cannulae with a curved tip will have a printed orientation line on the cannula body; do not use if line is missing or illegible. Orient the curved tip so the flow is directed superiorly, away from the aortic valve.
- Avoid pointing the cannula tip component directly toward the brachiocephalic arteries to minimize the possibility of directing any dislodged emboli into the arteries.
- DO NOT use a single EMBOL-X intra-aortic filter more than once. This may result in:
  1. Air embolism, since the porous plug on the filter plunger will vent only once;
  2. Increased risk of thrombus formation, which will make the filter difficult to insert and remove; and/or
  3. Distortion of the filter frame.
- Do not expose the device to organic solvents, ionizing radiation, ultraviolet light or alcohol-based fluids. The housing may weaken or crack and subsequent use may result in patient injury.
- Do not use the device if any of the components show signs of leakage.
- Anticoagulation should be routinely monitored during all CPB procedures.
- The EMBOL-X system should only be used in an operating room completely equipped for conventional cardiac surgery and by a surgeon trained in cardiac surgery.
- Position the EMBOL-X access device AT LEAST 1.5 centimeters away from the ostium of the brachiocephalic artery (towards the aortic valve), to reduce the risk of damaging the brachiocephalic ostium or obstructing bracheocephalic blood flow.
- Position the Aortic Cross Clamp AT LEAST 2.0 centimeters away from the EMBOL-X access device / EMBOL-X introducer sheath. Failure to do so may result in difficulty with insertion and removal of the filter.
- Failure to remove all air from the EMBOL-X intra-aortic filter may result in air embolism.
- Hold the EMBOL-X introducer sheath or base of the cannula component of the EMBOL-X access device while removing the obturator or inserting the EMBOL-X intra-aortic filter. Failure to do so may cause injury to the aorta.
- Do not manipulate the cannula component with the filter deployed. If the cannula must be manipulated, first retract the filter. Failure to do so may result in injury to the aorta.
- Do not use a single EMBOL-X intra-aortic filter for more than 60 (sixty) minutes. The EMBOL-X intra-aortic filter is for the temporary filtration of blood during cardiac surgery.
- The EMBOL-X intra-aortic filter must be retracted and removed from the EMBOL-X access device / EMBOL-X introducer sheath prior to routine administration of protamine for heparin reversal. Failure to do so may result in thrombus formation on the filter.
- If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X access device/aortic cannula can be removed. The EMBOL-X access device/aortic cannula can be removed with the EMBOL-X filter inserted using standard techniques.
- Although the EMBOL-X access device can be used separately in place of a standard arterial return cannula, the EMBOL-X intra-aortic filter must be used in conjunction with the EMBOL-X access device / EMBOL-X introducer sheath.
- Products are known to contain phthalates, which may be found in device materials containing plasticizers such as DEHP and BBP. High exposure to such phthalates during medical treatments in children and pregnant or nursing women may raise a concern. A review of available data and literature supports the conclusion that the benefits outweigh the overall residual risk.
- Dispose of used product in accordance with established hospital protocols for biohazards.

PRECAUTIONS

- Each Edwards Lifesciences device is packaged sterile and non-pyrogenic in a sealed, peel-type pouch.
- Exercise care during the connection of the cannula and the circuit to ensure that no air is trapped in the perfusion circuit.
- Placement, location, and orientation of the sutures in the aorta are critical to proper positioning of the EMBOL-X access device. Once the cannula component is secured with the sutures it is difficult to change the position of the EMBOL-X access device.
- Proper surgical procedures and techniques are the responsibility of the medical profession. Described procedures are provided for informational purposes only. Each physician must determine the appropriate use of this device for each patient based on medical training, experience, the type of procedure employed, and the benefits and risks associated with device use.

Warning: This device is designed, intended, and distributed for single use only. **Do not re-sterilize or reuse this device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.

COMPLICATIONS

Possible adverse effects include, but are not limited to, the following:

- Death
- Cardiac failure
- Stroke
- Aortic dissection or perforation
- Arterial thrombosis
- Plaque embolization
- Arrhythmia
- Excessive blood loss
- Wound infection, sepsis

DIRECTIONS FOR USE

WARNING: The EMBOL-X system should only be used in an operating room completely equipped for conventional cardiac surgery and by a surgeon trained in cardiac surgery.

Inspection Prior to Use

Prior to use, visually examine each device of the EMBOL-X system to verify that they have not been damaged. Do not use if device shows signs of damage (i.e., cuts, kinks, crushed areas), or if package is damaged or open.

Preparation for Insertion

- Visually estimate the diameter of the ascending aorta.
- Verify that there are no aneurysmal changes present in the ascending aorta.
- Select the appropriate size EMBOL-X intra-aortic filter based on the aortic diameter (refer to Table 1).

Table 1: EMBOL-X Arterial filter Sizes and Aortic Diameters

Arterial filter Sizes	**Minimum Aortic** Inner Diameter (mm)	Maximum Aortic Inner Diameter (mm)
XS	22	26
S	26	29
M	29	32
L	32	35
XL	35	40

Maximum Filter Deployment Time is 60min.

Preparation for Use (If using the filter with the EMBOL-X introducer sheath, follow the instructions provided in the Introducer Sheath Instructions for Use).The air in the lumens must be displaced prior to insertion to ensure that only fluid fills these lumens.

- Insert the obturator into the filter port of the EMBOL-X access device and verify that the locking connector snaps into place.
- Insert the vent plug into the proximal end of the cannula component of the EMBOL-X access device. Do not moisten the vent plug as this will prevent it from venting properly during insertion and de-airing. The vent plug is only able to vent once and will stop venting when fluid contacts it.

Insertion of the EMBOL-X Access Device

- Prepare the cardiopulmonary bypass circuit and prime with the appropriate solution.
- Moisten the cannula tip component of the EMBOL-X access device by submerging in sterile saline. DO NOT submerge the vent plug.
- Using the appropriate surgical technique, place purse string sutures at the desired cannulation site. A double purse string is recommended.
- Remove any loose tissue in the center of the purse sutures using forceps and/or scissors.

WARNING: Position the Access Device/Aortic Cannula AT LEAST 1.5 centimeters away from the ostium of the brachiocephalic artery (towards the aortic valve), to reduce the risk of damaging the brachiocephalic ostium or obstructing brachiocephalic blood flow.

WARNING: If used, position the Aortic Cross Clamp AT LEAST 2.0 centimeters away from the EMBOL-X access device / EMBOL-X introducer sheath. Failure to do so may result in difficulty with insertion and removal of the filter.

- Make an incision into the aorta in the area defined by the purse string sutures with an appropriate surgical blade.
- Insert the cannula component of the EMBOL-X access device into the incision, with a slight hooking motion, placing the curved tip away from the aortic valve.
- Assure penetration of the cannula tip component into the aorta by observing that the cannula body fills with blood. The cannula vent plug will prevent back bleeding during cannula component insertion.
- For cannulae marked with an orientation line, tip direction is indicated by referencing the orientation mark on the cannula body in relationship to the direction of flow as it exits the cannula tip. Orient the curved tip so the flow is directed superiorly, away from the aortic valve.
- Tighten the purse string sutures to stabilize the cannula body of the EMBOL-X access device ensuring that they are positioned in the cutouts on the flange.
- Ensure that the suture flange is positioned flat on the aorta and the cannula tip fully inserted into the aorta so that the filter port is perpendicular to the surface of the aorta.
- Remove the obturator slowly to de-air the filter lumen. Observe blood coming out through the valve. Replace the obturator and verify that it locks into place.
- Clamp the cannula body and remove the cannula vent plug from the cannula.
- Connect the cannula component to the arterial line of the extracorporeal CPB circuit.
- Remove all clamps from the cannula and lines prior to initiating cardiopulmonary bypass. Purge any remaining air in the cannula of the EMBOL-X access device and CPB circuit system.
- Initiate cardiopulmonary bypass. Refer to Diagram 2 for information on pressure drops across the EMBOL-X access device.

EMBOL-X Intra-aortic filter Preparation

- Remove the EMBOL-X intra-aortic filter from the package and inspect for any damage. If the EMBOL-X intra-aortic filter appears damaged, DO NOT USE.
- Thoroughly moisten the EMBOL-X intra-aortic filter by submerging it in a container of sterile saline and slowly swirling it around the container. This is intended to remove all air from the filter. DO NOT submerge the filter plunger knob as this will prevent it from venting properly once the filter is inserted. The filter vent knob will vent once and will stop venting once fluid contacts it.
- Retract the EMBOL-X intra-aortic filter fully into the cartridge while gently pinching the edges of the filter between your thumb and forefinger and guiding the edges of the filter upwards.

WARNING: Failure to remove all air from the EMBOL-X intra-aortic filter may result in air embolism.

Intra-aortic filter Insertion and Deployment

- Prepare the EMBOL-X intra-aortic filter prior to deployment as described above. The filter may be deployed at any time during the surgical procedure, once the patient is stabilized on cardiopulmonary bypass.

WARNING: Ensure that suture flange is flat on the surface of the aorta and the filter port is perpendicular to the surface of the aorta. Hold the EMBOL-X introducer sheath or base of the cannula component of the EMBOL-X access device while removing the obturator or inserting the EMBOL-X intra-aortic filter. Failure to do so may cause injury to the aorta.

- While holding the EMBOL-X introducer sheath or base of the cannula component of the EMBOL-X access device, to prevent force on the aorta, unlock the obturator and remove it from the filter port. The one-way valve will prevent excessive backbleeding.
- While still holding the EMBOL-X introducer sheath or base of the cannula component of the EMBOL-X access device, to prevent excessive force on the aorta, slowly insert the EMBOL-X intra-aortic filter cartridge into the filter port until an audible "click" is heard. The EMBOL-X intra-aortic filter is now locked in place.
- Confirm de-airing of the filter and cartridge by looking for blood in the knob of the plunger. If blood is not visible in the knob DO NOT INSERT the filter. Remove the EMBOL-X intra-aortic filter and insert a new one.
- Deploy the EMBOL-X intra-aortic filter by slowly pushing the plunger all the way down.
- The EMBOL-X intra-aortic filter may be left in place for up to 60 minutes to collect any emboli that may result from the clamping procedure or manipulation of the ascending aorta and heart during CPB surgery (EMBOL-X access device / EMBOL-X introducer sheath) or during other cardiac surgical procedures (EMBOL-X introducer sheath).

WARNING: Do not manipulate the cannula component of the EMBOL-X access device with the filter deployed. If the cannula component must be manipulated, first retract the EMBOL-X intra-aortic filter. Failure to do so may cause injury to the aorta.

WARNING: Do not use a single EMBOL-X intra-aortic filter for more than 60 (sixty) minutes. The EMBOL-X intra-aortic filter is for the temporary filtration of blood during cardiac surgery.

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EMBOL-X Intra-aortic filter Removal

- Hold the EMBOL-X introducer sheath or base of the cannula component of the EMBOL-X access device to stabilize the device.
- Fully retract the EMBOL-X intra-aortic filter into the cartridge by pulling on the plunger until it stops.

WARNING: If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X access device/aortic cannula can be removed. The EMBOL-X access device/aortic cannula can be removed with the EMBOL-X filter inserted using standard techniques.

- While holding onto the EMBOL-X introducer sheath or base of the cannula component of the EMBOL-X access device to prevent excessive force on the aorta, unlock and remove the EMBOL-X intra-aortic filter.
- Place the obturator back into the filter port and lock into place.

WARNING: DO NOT insert a single EMBOL-X intra-aortic filter more than once. This may result in: 1) air embolism, since the porous plug on the filter plunger will vent only once; 2) increased risk of thrombus formation, which will make the filter difficult to insert and remove; and/or 3) distortion of the filter frame.

EMBOL-X Access Device Removal

- Reduce the arterial flow rate until the patient is able to be completely weaned from cardiopulmonary bypass.
- Once the patient is stabilized, proceed with removal of the EMBOL-X access device.
- Loosen the sutures and remove the EMBOL-X access device from the aorta, simultaneously pulling the sutures tightly to accomplish hemostasis.

HOW SUPPLIED

The EMBOL-X system is individually packaged and provided separately. Both the EMBOL-X access device/aortic cannula and the EMBOL-X intra-aortic filter are provided STERILE and NON-PYROGENIC in unopened, undamaged package. The EMBOL-X access device/aortic cannula is sterilized by ethylene oxide. The EMBOL-X intra-aortic filter is sterilized by gamma radiation.

CONTENTS

The EMBOL-X access device aortic cannula and EMBOL-X intra-aortic filter are individually packaged and provided separately. The EMBOL-X access device/aortic cannula is packaged with a vent plug and a locking obturator.

STORAGE AND HANDLING

Store sterile packaged device in a cool, dry dark place until ready for use. Do not expose to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids.

For customer service, please contact Edwards Lifesciences LLC at the address below.

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Made in USA

FRANÇAIS

MODE D'EMPLOI

SYSTÈME DE PROTECTION EDWARDS EMBOL-X

Non commercialisé aux États-Unis

Voir les figures à la fin du mode d'emploi.

DESCRIPTION

Le système EMBOL-X est composé soit :

1. Du dispositif d'accès / canule aortique EMBOL-X (appelé ci-après dispositif d'accès EMBOL-X) et du filtre aortique EMBOL-X. OU
2. De la gaine d'introduction EMBOL-X et du filtre aortique EMBOL-X (se référer au mode d'emploi de la gaine d'introduction EMBOL-X).

Le système EMBOL-X avec le dispositif d'accès EMBOL-X est destiné à assurer le retour artériel du sang oxygéné provenant du circuit de circulation extra-corporelle (CEC) et à filtrer les micro-emboles de diamètre supérieur à 150 microns. Il est constitué d'une canule artérielle à deux lumières et d'un filtre aortique inséré dans l'aorte ascendante au cours de procédures utilisant la CEC. La première lumière de la canule assure l'entrée du sang artériel du circuit de CEC dans l'aorte ascendante et la deuxième lumière de la canule est destinée à l'insertion du filtre.

Le système EMBOL-X avec la gaine d'introduction EMBOL-X est destiné à filtrer les micro-emboles de diamètre supérieur à 150 microns. Il est constitué d'une gaine d'introduction à une lumière et d'un filtre aortique inséré dans l'aorte ascendante au cours de procédures requérant l'utilisation du filtre aortique EMBOL-X. La lumière est destinée à l'insertion du filtre

Le dispositif d'accès EMBOL-X est doté d'un embout distal de 24 FR (8 mm) avec un diamètre de débit réel de 22 FR (7,3 mm). L'extrémité proximale se raccorde aux tubulures de perfusion standard (3/8ème de pouce [9,5 mm] de diamètre) utilisées dans les circuits de CEC. Un obturateur de verrouillage, emballé avec la canule, permet de boucher la lumière du filtre pendant l'insertion du dispositif d'accès EMBOL-X lorsque le filtre n'est pas présent. La lumière du filtre est dotée d'une valve à sens unique destinée à réduire le reflux sanguin lors de l'insertion et retrait du filtre.

Le filtre aortique EMBOL-X, livré dans une cartouche qui se verrouille dans la lumière du filtre, s'insère par la lumière en appuyant sur un mécanisme à piston de type seringue. Le bouton de purge automatique permet d'évacuer automatiquement l'air de la cartouche lorsque cette dernière est insérée dans la canule/gaine d'introduction. Le filtre se retire en tirant sur le piston. À l'insertion, le filtre s'ouvre pour occuper le diamètre de l'aorte ascendante. Le filtre est conçu pour être inséré à tout moment, et de façon provisoire, lors d'interventions chirurgicales sous CEC (dispositif d'accès EMBOL-X / gaine d'introduction EMBOL-X) ou d'autres interventions de chirurgie cardiaque (gaine d'introduction EMBOL-X). Chaque filtre est utilisable pendant 60 minutes au maximum. Le filtre aortique EMBOL-X possède un revêtement hépariné (traitement Duraflo) pour éviter la formation de thrombus sur le filtre pendant son utilisation. Le filtre aortique EMBOL-X est disponible en plusieurs tailles, jusqu'à 40 mm au maximum, selon le diamètre de l'aorte.

USAGE PRÉVU / INDICATIONS D'EMPLOI

Le système EMBOL-X combine les fonctions d'une canule artérielle standard avec l'ajout d'un mécanisme de filtration servant à capturer les débris créés lors de la chirurgie cardiaque. Le dispositif d'accès / canule aortique EMBOL-X est destiné à la perfusion de l'aorte ascendante lors d'interventions chirurgicales sous CEC. Le filtre aortique EMBOL-X est conçu pour l'élimination des particules d'embole lors des interventions chirurgicales.

CONTRE-INDICATIONS

- Anévrisme de l'aorte ascendante
- Trauma aortique
- Aorte en porcelaine
- Les dispositifs à revêtement Duraflo sont contre-indiqués chez les patients présentant une sensibilité connue à l'héparine.

AVERTISSEMENTS

- Veiller à garder le capuchon de ventilation sec avant tout usage. Le capuchon de ventilation poreux est conçu pour ventiler l'air quand il est sec et pourra ne pas fonctionner normalement s'il est humide.
- Si les pressions dépassent les limites cliniques acceptables, vérifier la position de l'extrémité du dispositif et/ou la perméabilité de la canule
- Avec les produits à revêtement Duraflo, contrôler les temps de coagulation activée recommandés par le chirurgien, ou toute valeur équivalente, pendant la circulation extracorporelle pour assurer un niveau d'anticoagulation satisfaisant.
- La canule est destinée à une utilisation à court terme uniquement (moins de 6 h)
- Attacher solidement la jonction du raccord avec la canule avec une bande de sparadrap avant de commencer le pontage.
- Les canules renforcées par des fils métalliques doivent être clampées au niveau de la partie non renforcée située à l'extrémité du connecteur car le clampage de la partie renforcée pourrait déformer de façon permanente la canule, ce qui empêcherait alors le flux vers la canule et entrainerait un risque de perforation ou de déchirure de la canule.
- Utiliser toutes les précautions nécessaires lors de l'insertion du dispositif d'accès EMBOL-X lorsqu'il existe un risque de dissection du tissu aortique.
- Les canules dotées d'un embout incurvé ont leur corps imprimé d'une ligne d'orientation ; ne pas utiliser si cette ligne n'est pas présente ou si elle est effacée. Orienter l'embout incurvé de manière à ce que l'écoulement soit dirigé vers le haut, à l'écart de la valve aortique.
- Éviter de pointer l'embout de la canule vers les artères brachiocéphaliques afin de réduire le risque de diriger les emboles délogés vers les artères.
- NE PAS utiliser les filtres aortiques EMBOL-X plus d'une fois. Le non-respect de cette consigne peut provoquer :
  1. Une embolie gazeuse, car le capuchon poreux du piston du filtre n'évacue l'air qu'une seule fois;
  2. Un risque accru de formation d'un thrombus rendant l'insertion et le retrait du filtre difficile et/ou
  3. Une distorsion du cadre du filtre
- Ne pas exposer le dispositif à des solvants organiques, des radiations ionisantes, des rayons ultraviolets ni à des liquides alcoolisés. La structure peut se fragiliser ou se fissurer et tout usage ultérieur peut entrainer des blessures chez le patient.
- Ne pas utiliser le dispositif si l'un des composants montre des signes de fuite.
- Lors de procédures sous CEC, il convient de surveiller fréquemment l'anti-coagulation.
- Le système EMBOL-X doit uniquement être utilisé dans une salle d'opération équipée de manière complète pour la chirurgie cardiaque et par un chirurgien formé à la chirurgie cardiaque.
- Placer le dispositif d'accès EMBOL-X à AU MOINS 1,5 centimètre de l'orifice de l'artère brachiocéphalique (vers la valve aortique), afin de ne pas endommager l'orifice brachiocéphalique et de ne pas bloquer le débit sanguin brachiocéphalique.
- Placer le clamp latéral aortique à 2,0 centimètres AU MOINS du dispositif d'accès EMBOL-X / gaine d'introduction EMBOL-X. Le non-respect de cette consigne pourrait rendre l'insertion et le retrait du filtre difficiles.
- Il existe un risque d'embolie gazeuse si tout l'air contenu dans le filtre aortique EMBOL-X n'est pas évacué.
- Maintenir la gaine d'introduction EMBOL-X ou la base de la canule du dispositif d'accès EMBOL-X lors du retrait de l'obturateur ou de l'insertion du filtre aortique EMBOL-X. Le non-respect de cette consigne pourrait provoquer des lésions au niveau de l'aorte.
- Ne pas manipuler la canule avec le filtre déployé. Il convient de rétracter le filtre avant toute manipulation de la canule. Le non-respect de cette consigne pourrait provoquer des lésions au niveau de l'aorte.
- Ne pas utiliser les filtres aortiques simples EMBOL-X pendant plus de 60 (soixante) minutes. Le filtre aortique EMBOL-X est destiné à la filtration temporaire du sang lors d'interventions de chirurgie cardiaque.
- Le filtre aortique EMBOL-X doit être rétracté et retiré du dispositif d'accès EMBOL-X / gaine d'introduction EMBOL-X avant l'administration routinière de protamine pour l'inversion de l'héparine. Le non-respect de cette consigne pourrait entraîner la formation d'un thrombus sur le filtre.
- si une résistance se fait sentir lors de la rétraction du filtre intra-aortique EMBOL-X dans la cartouche, redéployer le filtre puis rétracter de nouveau le filtre intra-aortique EMBOL-X. Si une résistance supplémentaire se fait sentir, laisser le filtre en place jusqu'à ce que le dispositif d'accès/ la canule aortique EMBOL-X puisse être retiré(e). Le dispositif d'accès/la canule aortique EMBOL-X peut être retiré(e) à l'aide du filtre EMBOL-X inséré conformément aux techniques standard.
- Bien que le dispositif d'accès EMBOL-X soit utilisable séparément à la place d'une canule de retour artériel standard, le filtre aortique EMBOL-X doit être utilisé en association avec le dispositif d'accès EMBOL-X / gaine d'introduction EMBOL-X.
- l est connu que des produits contiennent des phtalates pouvant être retrouvés dans les matériaux du dispositif qui comprend des plastifiants tels que le DEHP et le BBP. Une forte exposition à ces phthalates au cours de traitements médicaux chez les enfants et les femmes enceintes ou allaitantes peut susciter une certaine inquiétude. Une revue des données et de la littérature disponibles étaye la conclusion selon laquelle les bénéfices l'emportent sur l'ensemble des risques résiduels.
- Jeter le produit usagé conformément aux protocoles établis par l'hôpital concernant les déchets biologiques.

PRÉCAUTIONS

- Chaque dispositif Edwards Lifesciences est conditionné de manière stérile et apyrogène dans une pochette hermétique pelable.
- Faire bien attention à ne pas emprisonner d'air dans le circuit de perfusion au moment de la connexion de la canule et du circuit.
- La localisation, l'emplacement et l'orientation des sutures dans l'aorte sont critiques pour le bon positionnement du dispositif d'accès EMBOL-X. Une fois que la canule est maintenue par les sutures, il est difficile de changer la position du dispositif d'accès EMBOL-X.
- Il appartient au corps médical d'appliquer des procédures et des techniques chirurgicales adéquates. Les procédures décrites sont uniquement fournies à titre indicatif. Chaque médecin doit déterminer, pour chaque patient, l'utilisation appropriée de ce dispositif en fonction de sa formation et de son expérience médicales, du type d'intervention exécutée ainsi qu'en fonction des avantages et risques associés à l'utilisation de ce dispositif.

Avertissement : Ce dispositif est conçu, prévu et distribué exclusivement pour un usage unique. **Ne pas restériliser ou réutiliser ce dispositif.** Il n'existe aucune donnée à l'appui de la stérilité, l'absence de pyrogénicité ou la fonctionnalité de cet appareil après un reconditionnement.

COMPLICATIONS

Liste non exhaustive des effets secondaires possibles :

- Décès
- Insuffisance cardiaque
- Accident vasculaire cérébral
- Dissection ou perforation aortique
- Thrombose artérielle
- Thromboembolie
- Arythmie
- Perte excessive de sang
- Septicémie/infection au niveau de la plaie

MODE D'EMPLOI

MISE EN GARDE : le système EMBOL-X doit uniquement être utilisé dans une salle d'opération équipée de manière complète pour la chirurgie cardiaque et par un chirurgien formé à la chirurgie cardiaque.

Examen avant l'utilisation

Avant toute utilisation, vérifier que chaque dispositif du système EMBOL-X est intact. Ne pas utiliser si le produit est endommagé (coupures, plures, écrasement) ou si son emballage a été ouvert ou est endommagé.

Préparation pour l'insertion

- Effectuer une estimation visuelle du diamètre de l'aorte ascendante.
- Vérifier qu'il n'y a présence d'aucun changement anévrismal dans l'aorte ascendante.
- Sélectionner la taille appropriée du filtre aortique EMBOL-X par rapport au diamètre aortique (se référer au tableau 1).

Tableau 1 : tailles des filtres artériels EMBOL-X et diamètres aortiques

Filtre artériel Tailles	Diamètre interne minimum (mm)	Diamètre interne maximum (mm)
XS	22	26
S	26	29
M	29	32
L	32	35
XL	35	40

Le temps de déploiement maximal du filtre est de 60 min.

Préparation pour l'utilisation (Si le filtre avec la gaine d'introduction EMBOL-X est utilisé, suivre les instructions fournies dans le mode d'emploi de la gaine d'introduction).

L'air contenu dans les lumières doit être chassé avant insertion pour s'assurer que seul du liquide remplit ces lumières.

- Insérer l'obturateur dans l'orifice du filtre du dispositif d'accès EMBOL-X et vérifier que le connecteur de verrouillage se rabat en position.
- Insérer le capuchon de ventilation dans l'extrémité proximale de la canule du dispositif d'accès EMBOL-X. Ne pas mouiller le capuchon de ventilation, cela risquerait de réduire l'efficacité de la purge lors de l'insertion et de l'évacuation de l'air. Le capuchon de ventilation ne peut effectuer qu'une seule purge et s'arrête d'évacuer l'air au contact de fluide.

Insertion du dispositif d'accès EMBOL-X

- Préparer le circuit de circulation extracorporelle et ajouter la solution appropriée.
- Mouiller l'embout de la canule du dispositif d'accès EMBOL-X en l'immergeant dans du sérum physiologique. NE PAS immerger le capuchon de ventilation.
- À l'aide de la technique chirurgicale appropriée, pratiquer des sutures en bourse sur le site de canulation désiré. Une double suture en bourse est recommandée.
- Retirer tout tissu lâche au centre des sutures en bourse à l'aide de pinces et/ou de ciseaux.

MISE EN GARDE : placer le dispositif d'accès/canule aortique à AU MOINS 1,5 centimètre de l'orifice de l'artère brachiocéphalique (vers la valve aortique), afin de ne pas endommager l'orifice brachiocéphalique et de ne pas bloquer le débit sanguin brachiocéphalique.

MISE EN GARDE : le cas échéant, placer le clamp latéral aortique à 2,0 centimètres AU MOINS du dispositif d'accès EMBOL-X / gaine d'introduction EMBOL-X. Le non-respect de cette consigne pourrait rendre l'insertion et le retrait du filtre difficiles.

- À l'aide d'une lame chirurgicale appropriée, pratiquer une incision dans l'aorte, dans la zone définie par les sutures en bourse.
- Insérer la canule du dispositif d'accès EMBOL-X dans l'incision, à l'aide d'un léger mouvement de crochet, en éloignant l'embout incurvé de la valve aortique.
- S'assurer que l'embout de la canule est bien placé dans l'aorte en vérifiant que le corps de la canule se remplit de sang. Le capuchon de ventilation empêche le reflux sanguin pendant l'insertion de la canule.
- Pour les canules repérées d'une ligne d'orientation, la direction de l'embout est indiquée en positionnant le repère d'orientation sur le corps de la canule, dans la direction de l'écoulement à la sortie de l'embout. Orienter l'embout incurvé de manière à ce que l'écoulement soit dirigé vers le haut, à l'écart de la valve aortique.
- Serrer les sutures en bourse afin d'immobiliser le corps de la canule du dispositif d'accès EMBOL-X en s'assurant que celles-ci sont correctement positionnées dans les encoches de la collerette.
- S'assurer que la collerette de suture est positionnée à plat sur la surface de l'aorte et que l'embout de la canule est complètement inséré dans l'aorte de manière à ce que l'orifice du filtre soit perpendiculaire à la surface de l'aorte.
- Retirer lentement l'obturateur afin d'évacuer l'air de la lumière du filtre. Observer le sang sortir de la valve. Replacer l'obturateur et vérifier qu'il est bien verrouillé en position.
- Clamper le corps de la canule et retirer le capuchon de ventilation de la canule.
- Raccorder la canule à la ligne artérielle du circuit extra-corporel (CEC).
- Retirer toutes les pinces de la canule et des lignes du circuit avant de démarrer la circulation extracorporelle. Évacuer

le reste d'air contenu dans la canule du dispositif d'accès EMBOL-X et du système du circuit CEC.
- Démarrer la circulation extracorporelle. Se référer au schéma 2 pour les informations concernant les chutes de pression présentes à travers le dispositif d'accès EMBOL-X.

Préparation du filtre aortique EMBOL-X

- Retirer le filtre aortique EMBOL-X de l'emballage et vérifier l'absence de détérioration. Si le filtre aortique EMBOL-X est endommagé, NE PAS L'UTILISER.
- Mouiller abondamment le filtre aortique EMBOL-X en l'immergeant dans un conteneur rempli de sérum physiologique stérile et en le faisant tourbillonner à l'intérieur du conteneur. Cette action est destinée à évacuer l'air du filtre. NE PAS immerger le bouton de purge du filtre, cela risquerait de compromettre l'efficacité de l'évacuation de l'air une fois le filtre inséré. Le bouton de purge du filtre ne peut effectuer qu'une seule purge et s'arrête d'évacuer l'air au contact de fluide.
- Rétracter complètement le filtre aortique EMBOL-X dans la cartouche en pinçant délicatement les bords du filtre entre le pouce et l'index puis en guidant les bords du filtre vers le haut.

MISE EN GARDE : il existe un risque d'embolie gazeuse si tout l'air contenu dans le filtre aortique EMBOL-X n'est pas évacué.

Insertion et déploiement du filtre aortique

- Préparer le filtre aortique EMBOL-X avant le déploiement tel que décrit ci-dessus. Une fois le patient stabilisé par circulation extracorporelle, le filtre peut être déployé à n'importe quel moment au cours de la procédure chirurgicale.

MISE EN GARDE : s'assurer que la collerette de suture est positionnée à plat sur la surface de l'aorte et que l'orifice du filtre est perpendiculaire à la surface de l'aorte. Maintenir la gaine d'introduction EMBOL-X ou la base de la canule du dispositif d'accès EMBOL-X lors du retrait de l'obturateur ou de l'insertion du filtre aortique EMBOL-X. Le non-respect de cette consigne pourrait provoquer des lésions au niveau de l'aorte.

- Tout en maintenant la gaine d'introduction EMBOL-X ou la base de la canule du dispositif d'accès EMBOL-X pour éviter d'exercer des contraintes sur l'aorte, déverrouiller l'obturateur et le retirer de l'orifice du filtre. La valve anti-retour empêche le retour excessif de sang.
- Toujours en maintenant la gaine d'introduction EMBOL-X ou la base de la canule du dispositif d'accès EMBOL-X pour éviter des contraintes excessives sur l'aorte, insérer doucement la cartouche du filtre aortique EMBOL-X dans l'orifice du filtre jusqu'à entendre un « clic ». Le filtre aortique EMBOL-X est désormais verrouillé en position.
- Confirmer l'évacuation de l'air du filtre et de la cartouche en vérifiant la présence de sang dans le bouton du piston. S'il n'y pas de sang visible dans le bouton, NE PAS INSÉRER le filtre. Retirer le filtre aortique EMBOL-X et en insérer un nouveau.
- Déployer le filtre aortique EMBOL-X en poussant lentement sur le piston jusqu'au maximum.
- Le filtre aortique EMBOL-X peut rester en place jusqu'à 60 minutes pour récupérer les emboles éventuels résultant de la procédure de clampage ou de la manipulation de l'aorte ascendante et du cœur lors de l'intervention chirurgicale sous CEC (dispositif d'accès EMBOL-X / gaine d'introduction EMBOL-X) ou de toute autre intervention de chirurgie cardiaque (gaine d'introduction EMBOL-X).

MISE EN GARDE : ne pas manipuler la canule du dispositif d'accès EMBOL-X avec le filtre déployé. Il convient de rétracter le filtre aortique EMBOL-X avant toute manipulation de la canule. Le non-respect de cette consigne pourrait provoquer des lésions au niveau de l'aorte.

MISE EN GARDE : ne pas utiliser un filtre aortique simple EMBOL-X pendant plus de 60 (soixante) minutes. Le filtre aortique EMBOL-X est destiné à la filtration temporaire du sang lors d'interventions de chirurgie cardiaque.

Retrait du filtre aortique EMBOL-X

- Maintenir la gaine d'introduction EMBOL-X ou la base de la canule du dispositif d'accès EMBOL-X pour immobiliser le dispositif.
- Rétracter complètement le filtre aortique EMBOL-X dans la cartouche en tirant sur le piston jusqu'à ce qu'il se bloque.

MISE EN GARDE : si une résistance se fait sentir lors de la rétraction du filtre intra-aortique EMBOL-X dans la cartouche, redéployer le filtre puis rétracter de nouveau le filtre intra-aortique EMBOL-X. Si une résistance supplémentaire se fait sentir, laisser le filtre en place jusqu'à ce que le dispositif d'accès/la canule aortique EMBOL-X puisse être retiré(e). Le dispositif d'accès/la canule aortique EMBOL-X peut être retiré(e) à l'aide du filtre EMBOL-X inséré conformément aux techniques standard.

- Tout en maintenant la gaine d'introduction EMBOL-X ou la base de la canule du dispositif d'accès EMBOL-X pour éviter des contraintes excessives sur l'aorte, déverrouiller le filtre aortique EMBOL-X et le retirer.
- Remettre l'obturateur dans l'orifice du filtre et le verrouiller en position.

MISE EN GARDE : NE PAS utiliser un filtre aortique simple EMBOL-X plus d'une fois. Le non-respect de cette consigne peut provoquer : 1) une embolie gazeuse, car le capuchon poreux situé sur le piston du filtre n'évacue l'air qu'une seule fois ; 2) un risque accru de formation d'un thrombus rendant l'insertion et le retrait du filtre difficile et/ou 3) une déformation du cadre du filtre.

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Retrait du dispositif d'accès EMBOL-X

- Réduire le débit artériel jusqu'à ce que le patient soit capable de se passer complètement de la circulation extracorporelle.
- Une fois le patient stabilisé, procéder au retrait du dispositif d'accès EMBOL-X.
- Desserrer les sutures et retirer le dispositif d'accès EMBOL-X de l'aorte tout en tirant fermement sur les sutures afin d'obtenir l'hémostase

PRÉSENTATION

Le système EMBOL-X est emballé individuellement et fourni séparément. Le système d'accès/la canule aortique EMBOL-X (dispositif d'accès / canule aortique et filtre aortique) et le filtre aortique EMBOL-X sont fournis STÉRILES et APYROGÈNES à condition que l'emballage soit fermé et intact. Le dispositif d'accès/canule aortique EMBOL-X est stérilisé à l'oxyde d'éthylène. Le filtre aortique EMBOL-X est stérilisé par rayonnement gamma.

CONTENU

La canule aortique du dispositif d'accès EMBOL-X et le filtre aortique EMBOL-X sont emballés individuellement et fournis séparément. Le dispositif d'accès/canule aortique EMBOL-X est emballé avec un capuchon de ventilation et un obturateur de verrouillage.

CONSERVATION ET MANIPULATION

Conserver le dispositif dans son emballage stérile dans un endroit frais, sombre et sec, jusqu'à son utilisation. Ne pas l'exposer à des solvants organiques, des radiations ionisantes, des rayons ultraviolets ni à des liquides alcoolisés.

Pour le service clientèle, veuillez contacter Edwards Lifesciences LLC à l'adresse ci-dessous.

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Pour toute information relative aux produits ou pour toute question concernant la vente et la réparation, veuillez directement contacter Edwards Lifesciences LLC.

EXCLUSION DE GARANTIE

EDWARDS LIFESCIENCES N'ÉMET AUCUNE GARANTIE EXPRESSE OU IMPLICITE CONCERNANT LE(S) PRODUIT(S) VENDU(S) CI-DESSOUS, Y COMPRIS AUCUNE GARANTIE IMPLICITE DE QUALITÉ MARCHANDE OU D'ADAPATION À UNE FIN QUELCONQUE, ET EN REJETTE EXPRESSÉMENT TOUTE GARANTIE. DANS LA MESURE OÙ LES DESCRIPTIONS ET/OU LES SPÉCIFICATIONS DU PRODUIT SONT PRÉSENTES DANS CE DOCUMENT, LESDITES SPÉCIFICATIONS ET/OU DESCRIPTIONS SONT À CONSIDÉRER COMME LANGAGE GÉNÉRAL ET NE CONSTITUENT EN AUCUN CAS UNE GARANTIE QUE LE PRODUIT SOIT CONFORME À LA DESCRIPTION ET/OU À LA SPÉCIFICATION DU PRODUIT.

Fabriqué aux États-Unis

APPENDIX H: Embol-X System Introducer Sheath Instructions for Use

Edwards Lifesciences
ThruPort™ Systems

EMBOL-X INTRODUCER SHEATH

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Figure 1. EMBOL-X Introducer Sheath 20

ENGLISH

Caution: Federal law (USA) restricts this device to sale by or on the order of a physician.

See Figure at the end of the Instructions for Use.

DESCRIPTION

The EMBOL-X™ Introducer Sheath is indicated for use in procedures requiring the introduction of EMBOL-X Intra-Aortic Filters. The Introducer Sheath consists of a single-lumen Introducer and a removable self venting snap-lock Obturator.

Insertion Diameter	Internal Diameter	Effective Length of Introducer w/o Obturator	Effective Length of Introducer w/ Obturator
17 FR max (5.7mm)	14 FR min (4.7mm)	5.5mm	12.8mm

Note: All dimensions are nominal unless otherwise specified.

The Introducer contains an internal one-way valve designed to minimize backbleeding when the EMBOL-X Intra-Aortic Filter or the Obturator is not in place. The Obturator's distal tip is tapered. With the Obturator in place, the tapered tip helps facilitate the entry of the Introducer into the vessel. The Obturator also prevents back bleeding when in place and vents air through vent grooves in its shaft that lead to a vent plug. The Obturator is removed only when intravascular access with a Filter is necessary. The Introducer contains a keyed snap-lock with orientation markings on the Introducer housing and suture flange. The keyed snap-lock holds the Obturator in place. The orientation markings give the user a visual cue of the orientation of the Introducer. The Introducer Sheath enters a vessel by means of a surgical incision made by the physician using standard surgical techniques. The Introducer contains a suture flange at its distal tip to provide added stability and for suture attachment. Only the portion distal to the flange enters the vessel. Suture rings are also provided on the Introducer housing to provide additional stability, if necessary.

Refer to the Instructions for Use included with the Embol-X Filter for specific Embol-X Filter information including indications, warnings, precautions, sizing, and detailed instructions for use.

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NOTE: The EMBOL-X Filter is not indicated for use if the Aortic inner diameter is smaller than 22 mm or larger than 40 mm.

INDICATIONS FOR USE

The EMBOL-X™ Introducer Sheath is indicated for use in procedures requiring the introduction of EMBOL-X Intra-Aortic Filters.

CONTENTS

The Introducer Sheath consists of an Introducer and an Obturator.

HOW SUPPLIED

Each Introducer Sheath is packaged sterile and non-pyrogenic in a sealed, peel-type pouch. Do not use if the product shows signs of damage (i.e., cuts, kinks, crushed areas), or if package is damaged or open.

STORAGE AND HANDLING

Store sterile packaged product in a cool dry place until ready for use. DO NOT expose to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids.

CONTRAINDICATIONS

- Aortic aneurysm
- Aortic trauma
- In patients who are unable to receive anticoagulation therapy.

WARNINGS AND PRECAUTIONS

The Introducer Sheath is designed, intended, and distributed for single use only. DO NOT RE-STERILIZE or REUSE this product. There are no data to support the sterility, nonpyrogenicity, and functionality of the Introducer Sheath after reprocessing.

Use extreme caution when inserting the Introducer Sheath if there is a possibility of tissue dissection of the vessel.

When the Introducer Sheath is in situ, the Introducer must be held when manipulating the Obturator or Filter. Failure to do so may cause injury to the vessel.

Position the Introducer Sheath AT LEAST 1.5 centimeters proximally to the ostium of the brachiocephalic artery (towards the aortic valve), to reduce the risk of damaging the brachiocephalic ostium or obstructing brachiocephalic blood flow.

Ensure that the Introducer is inserted so that the orientation markings are pointed in the retrograde direction. Failure to do so may result in incorrect positioning of the Filter.

When using the Introducer Sheath with the Filter during a Cardiopulmonary Bypass (CPB) cardiac procedure, position the full or partial aortic cross clamps AT LEAST 2.0 centimeters proximal to the Introducer. Failure to do so may result in difficulty with deployment and retrieval of the Filter.

Monitor anticoagulation routinely during all procedures.

Do not expose the Introducer Sheath to organic solvents, ionizing radiation, ultraviolet light or alcohol-based fluids. The Introducer Sheath may weaken or crack, and subsequent use may result in patient injury.

Placement, location, and orientation of the sutures in the vessel are critical to proper positioning of the Introducer. Once the Introducer is secured with the sutures it is difficult to change the position of the Introducer.

Proper surgical procedures and techniques are the responsibility of the medical profession. Described procedures are provided for informational purposes only. Each physician must determine the appropriate use of this Introducer Sheath for each patient based on medical training, experience, the type of procedure employed, and the benefits and risks associated with product use.

COMPLICATIONS

Possible adverse effects include, but are not limited to, the following:

- Arterial thrombosis
- Plaque embolization
- Air embolism
- Excessive blood loss
- Wound infection
- Sepsis
- Vascular dissection or perforation

INSTRUCTIONS FOR USE

WARNING: The Introducer Sheath should be used only in an operating room completely equipped for cardiac surgery and by a surgeon trained in cardiac surgery

1. Inspection Prior to Use

- Prior to opening and use, visually examine:
  - The package integrity. If the package's sterile barrier appears to have been jeopardized, DO NOT USE
  - The Introducer Sheath to verify that it has not been damaged. If the product appears damaged, DO NOT USE.

2. Preparation for use of the Introducer Sheath

- After inspection, carefully insert the Obturator into the Introducer and verify that the snap-lock connector snaps into place. Inspect the Obturator in the introducer and verify easy removal by releasing the locking mechanism and pulling the obturator out of the lumen.
- Carefully re-insert the Obturator.

3. Insertion of the Introducer Sheath

- Moisten the tip of the Introducer Sheath by submerging it in sterile saline.
- Using the appropriate surgical technique, place purse string sutures at the desired insertion site.
- Remove any loose tissue in the center of the purse string sutures using forceps and/or scissors.

WARNING: When selecting access site, the physician should be aware of the Introducer and Obturator effective lengths so as not to cause trauma to the posterior wall of the vessel.

WARNING: Position the Introducer Sheath AT LEAST 1.5 centimeters proximal to the ostium of the brachiocephalic artery (towards the aortic valve) to reduce the risk of damaging the brachiocephalic ostium or obstructing brachiocephalic blood flow.

WARNING: When using the Introducer Sheath with the Filter during a Cardiopulmonary Bypass (CPB) cardiac procedure, position the full or partial aortic cross clamps AT LEAST 2.0 centimeters proximal to the Introducer. Failure to do so may result in difficulty with deployment and retrieval of the Filter.

WARNING: When using the Introducer Sheath with the Filter during a Cardiopulmonary Bypass (CPB) cardiac procedure, the Introducer must be positioned proximal to the aortic perfusion cannula, i.e. between the aortic perfusion cannula and the heart. Failure to do so may result in premature thrombus formation on the Filter.

- With an appropriate surgical blade, make an incision into the vessel in the area defined by the purse string sutures.
- Insert the Introducer Sheath into the incision.
- Ensure that the suture flange is positioned flat on the aorta and the Introducer Sheath tip is fully inserted into the aorta so that the Introducer Sheath is perpendicular to the surface of the aorta.

WARNING: Ensure that the Introducer is inserted so that the orientation markings are pointed in the retrograde direction as shown in Figure 1. Failure to do so may result in incorrect positioning of the Filter.

- Tighten the purse string sutures to stabilize the Introducer Sheath, ensuring that they are positioned in the suture slot on the flange. Suture rings are also provided on the Introducer housing to provide additional stability, if necessary.
- The air in the Introducer must be purged prior to introduction of the Filter to ensure that only fluid fills this lumen. To achieve this, ensure that air has vented through the Obturator. When the Obturator has filled with blood, retract it slightly to allow the Obturator vent grooves to breach the Introducer valve. Continue to carefully adjust the Obturator until complete air venting has been achieved. Blood should visibly fill the Introducer. This will also assure the penetration of the Introducer into the vessel.
- Carefully re-insert the Obturator.

WARNING: Hold the Introducer while removing the Obturator or inserting the Filter. Failure to do so may cause injury to the vessel.

4. Filter Introduction

- Prior to using the Introducer, refer to the Filter Instructions for Use for any specific instructions, precautions, or warnings.
- Unlock the Obturator and remove it from the Introducer. The one-way valve will prevent excessive backbleeding.

WARNING: Hold the Introducer while removing the Obturator or inserting the Filter. Failure to do so may cause injury to the vessel.

- While holding the Introducer to prevent excessive force on the vessel, slowly insert the Filter into the Introducer. An audible "click" will be heard when the Filter is "locked" in place.

5. Filter Retraction and Removal

- Hold the Introducer to provide stabilization and prevent excessive force on the vessel.
- While holding the Introducer, unlock the snap lock and gently withdraw the Filter. Refer to the manufacturer Instructions for Use for any specific instructions, precautions, or warnings.

WARNING: If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X introducer sheath can be removed. The EMBOL-X introducer sheath can be removed with the EMBOL-X filter inserted using standard techniques.

- Upon Filter removal, place the Obturator back into the Introducer and lock into place.

6. Introducer Sheath Removal

- When appropriate, loosen the sutures and remove the Introducer Sheath from the vessel, simultaneously pulling the sutures tightly to achieve hemostasis.

PRODUCT DISPOSAL

Dispose of used product in accordance with established hospital protocols for biohazards.

TECHNICAL ASSISTANCE

For technical assistance, please call Edwards Technical Support at the following telephone numbers:

Inside the U.S. and Canada
(24 hours): 800.822.9837
Outside the U.S. and Canada
(24 hours): 949.250.2222
In the UK: .....0870 606 2040 - Option 4
In Ireland: .....01 8211012 Option 4

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FRANÇAIS

Attention : les lois fédérales des États-Unis limitent la vente de ce dispositif à un médecin ou sur prescription d'un médecin.

Consulter la figure à la fin du mode d'emploi.

DESCRIPTION

La gaine d'introduction EMBOL-X™ est indiquee pour une utilisation dans les procedures requerant l'introduction de filtres intra-aortiques EMBOL-X. La gaine d'introduction se compose d'un introducteur à lumière simple et d'un obturateur amovible à aération automatique et clapet de fermeture.

Diamètre d'insertion	Diamètre interne	Longueur utile de l'introducteur sans obturateur	Longueur utile de l'intro-ducteur avec obturateur
17 FR maxi (5,7 mm)	14 FR maxi (4,7 mm)	5,5 mm	12,8 mm

Remarque : Toutes les dimensions sont nominales, sauf indications contraires.

L'introducteur contient une valve unidirectionnelle interne conçue pour réduire le saignement rétrograde lorsque le filtre intra-aortique EMBOL-X ou l'obturateur n'est pas en place. L'embout distal de l'obturateur est conique. Lorsque l'obturateur est en place, l'embout conique permet de faciliter l'insertion de l'introducteur dans le vaisseau. L'obturateur permet également

d'éviter le saignement rétrograde lorsqu'il est en place et il évacue l'air par des rainures d'aération pratiquées dans sa tige pour amener l'air vers un bouchon d'aération. L'obturateur est uniquement retiré lorsqu'un accès intravasculaire à l'aide d'un filtre est nécessaire. L'introducteur contient un clapet de fermeture à encoche avec des repères d'orientation sur le logement de l'introducteur et une bride de suture. Le clapet de fermeture à encoche maintient l'obturateur en place. Les repères d'orientation permettent à l'utilisateur de visualiser l'orientation de l'introducteur. La gaine d'introduction est insérée dans un vaisseau en pratiquant une incision chirurgicale réalisée par un chirurgien selon les techniques chirurgicales courantes. Une bride de suture se trouve sur l'extrémité distale de l'introducteur afin d'en accroître la stabilité et d'y fixer une suture. Seule la partie distale de la bride pénètre dans le vaisseau. Des bagues de suture sont également fournies sur le logement de l'introducteur, pour plus de stabilité, si nécessaire.

Se reporter au mode d'emploi fourni avec le Filtre Embol-X pour les informations spécifiques au Filtre Embol-X couvrant les indications, les avertissements, les précautions, le dimensionnement et le mode d'emploi détaillé.

Remarque : Le Filtre EMBOL-X n'est pas indiqué pour une utilisation si le diamètre aortique interne est inférieur à 22 mm ou supérieur à 40 mm.

MODE D'EMPLOI

La gaine d'introduction EMBOL-X™ est indiquée pour une utilisation dans les procédures requérant l'introduction de filtres intra-aortiques EMBOL-X.

TABLE DES MATIÈRES

La gaine d'introduction se compose d'un introducteur et d'un obturateur.

CONDITIONNEMENT

Chaque gaine d'introduction est conditionnée de manière stérile et apyrogène dans une poche hermétique pelable. Ne pas utiliser si le produit est endommagé (coupures, pliures, écrasement) ou si l'emballage est ouvert ou endommagé.

CONSERVATION ET MANIPULATION

Conserver le produit dans son emballage stérile dans un endroit frais et sec, jusqu'à son utilisation. NE PAS l'exposer à des solvants organiques, des radiations ionisantes, des rayons ultraviolets ni à des liquides alcoolisés.

CONTRE-INDICATIONS

- Anévrisme aortique
- Trauma aortique
- Chez les patients qui ne peuvent pas recevoir de traitement anticoagulant.

AVERTISSEMENTS ET PRÉCAUTIONS

La gaine d'introduction est conçue, prévue et distribuée exclusivement pour un usage unique. NE PAS RESTÉRILISER ni RÉUTILISER ce produit. Il n'existe aucune donnée garantissant la stérilité, l'absence de pyrogénicité ou la fonctionnalité de la gaine d'introduction après un retraitement.

Faire extrêmement attention lors de l'insertion de la gaine d'introduction dans le cas d'une possibilité de dissection tissulaire du vaisseau.

Lorsque la gaine d'introduction est en place, l'introducteur doit être tenu lors de la manipulation de l'obturateur ou du filtre. Le non-respect de cette recommandation risquerait d'endommager le vaisseau.

Placer la gaine d'introduction à AU MOINS 1,5 centimètre en amont de l'orifice de l'artère brachiocéphalique (vers la valve aortique), afin de ne pas endommager l'orifice brachiocéphalique et de ne pas bloquer le débit sanguin brachiocéphalique.

S'assurer que l'introducteur est inséré de manière à ce que les repères d'orientation soient pointés en direction rétrograde. Le non-respect de cette recommandation pourrait entraîner le mauvais positionnement du filtre.

Quand la gaine d'introduction est utilisée avec le filtre lors d'une procédure cardiaque de circulation extracorporelle, placer les clamps aortiques complets ou partiels à AU MOINS 2,0 centimètres en amont de l'introducteur. Le non-respect de cette recommandation pourrait rendre le déploiement et le retrait du filtre plus difficiles.

Contrôler régulièrement l'anticoagulation pendant toutes les procédures.

Ne pas exposer la gaine d'introduction à des solvants organiques, des radiations ionisantes, des rayons ultraviolets ni à des liquides alcoolisés. La gaine d'introduction peut se fragiliser ou se fissurer et tout usage ultérieur peut entraîner des blessures chez le patient.

La localisation, l'emplacement et l'orientation des sutures dans le vaisseau sont critiques pour le bon positionnement de l'introducteur. Une fois que l'introducteur est fixé à l'aide des sutures il est difficile d'en changer la position.

Il appartient au corps médical d'appliquer des procédures et des techniques chirurgicales adéquates. Les procédures décrites sont uniquement fournies à titre indicatif. Chaque médecin doit déterminer, pour chaque patient, l'utilisation appropriée de cette gaine d'introduction en fonction de sa formation et de son expérience médicales, du type d'intervention exécutée et en fonction des bénéfices et risques associés à l'utilisation de ce produit.

COMPLICATIONS

Liste non exhaustive des effets secondaires possibles :

- thrombose artérielle
- thromboembolie
- embolie gazeuse
- perte excessive de sang
- infection de la cicatrice
- septicémie
- dissection ou perforation vasculaire

MODE D'EMPLOI

AVERTISSEMENT : La gaine d'introduction sera uniquement utilisée dans une salle d'opération équipée d'une manière complète pour la chirurgie cardiaque, par un chirurgien formé à la chirurgie cardiaque.

1. Examen avant l'utilisation

- Avant l'ouverture et l'utilisation, examiner visuellement :
  - l'intégrité de l'emballage. Si les barrières stériles de l'emballage paraissent compromises, NE PAS UTILISER.
  - la gaine d'introduction avant de s'être assuré qu'elle n'est pas endommagée. Si le produit semble endommagé, NE PAS L'UTILISER.

2. Préparation à l'utilisation de la gaine d'introduction

- Après l'inspection, insérer soigneusement l'obturateur dans l'introducteur et vérifier que le clapet de fermeture se met en place. Inspecter l'obturateur dans l'introducteur et vérifier qu'il se retire facilement en libérant le mécanisme de verrouillage et en tirant l'obturateur en dehors de la lumière.
- Réinsérer prudemment l'obturateur.

3. Insertion de la gaine d'introduction

- Humidifier l'embout de la gaine d'introduction en l'immergeant dans du sérum physiologique.
- À l'aide de la technique chirurgicale appropriée, pratiquer des sutures en bourse sur le site d'insertion désiré.
- Retirer tout tissu lâche au centre des sutures en bourse à l'aide de pinces et/ou de ciseaux.

AVERTISSEMENT : Lors du choix du site d'accès, le chirurgien doit faire attention aux longueurs utiles de l'introducteur et de l'obturateur afin de ne pas traumatiser la paroi postérieure du vaisseau.

AVERTISSEMENT : Placer la gaine d'introduction à AU MOINS 1,5 centimètre en amont de l'orifice de l'artère brachiocéphalique (vers la valve aortique), afin de ne pas endommager l'orifice brachiocéphalique et de ne pas bloquer le débit sanguin brachiocéphalique.

AVERTISSEMENT : Quand la gaine d'introduction est utilisée avec le filtre lors d'une procédure cardiaque sous circulation extracorporelle, placer les clamps aortiques latéraux ou partiels à AU MOINS 2,0 centimètres en amont de l'introducteur. Le non-respect de cette recommandation pourrait rendre le déploiement et le retrait du filtre plus difficiles.

AVERTISSEMENT : En cas d'utilisation de la gaine d'introduction avec le filtre intra-aortique au cours d'une procédure cardiaque de circulation extracorporelle, l'introducteur doit être placé en position proximale par rapport à la canule de perfusion aortique, c.-à-d. entre la canule de perfusion aortique et le cœur. Le non-respect de cette recommandation peut entraîner la formation prématurée d'une thrombose sur le filtre.

- À l'aide d'une lame chirurgicale appropriée, pratiquer une incision dans le vaisseau, dans la zone définie par les sutures en bourse.
- Insérer la gaine d'introduction dans l'incision.
- S'assurer que la bride de suture est positionnée à plat sur l'aorte et que l'embout de la gaine introductrice est entièrement inséré dans l'aorte de manière à ce que la gaine introductrice soit perpendiculaire à la surface de l'aorte.

AVERTISSEMENT : S'assurer que l'introducteur est inséré de manière à ce que les repères d'orientation soient pointés en direction rétrograde comme dans la figure 1. Le non-respect de cette recommandation pourrait entraîner le mauvais positionnement du filtre.

- Serrer les sutures en bourse pour stabiliser la gaine d'introduction en s'assurant que les sutures sont positionnées dans la fente de suture de la bride. Des bagues de suture sont également fournies sur le logement de l'introducteur, pour plus de stabilité, si nécessaire.
- Purger l'air dans l'introducteur avant d'insérer le filtre afin de s'assurer que seuls des fluides remplissent cette lumière. Pour cela, s'assurer que l'air est évacué par l'obturateur. Lorsque l'obturateur est rempli de sang, le rétracter légèrement afin de permettre aux rainures de l'évent d'obturateur de s'insérer dans la valve de l'introducteur. Continuer d'ajuster prudemment l'obturateur jusqu'à la purge complète de l'air. Le sang doit visiblement remplir l'introducteur. Cela garantira également la pénétration de l'introducteur dans le vaisseau.
- Réinsérer prudemment l'obturateur.

AVERTISSEMENT : Maintenir l'introducteur pendant le retrait de l'obturateur ou l'insertion du filtre. Le non-respect de cette recommandation risquerait d'endommager le vaisseau.

4. Introduction du filtre

- Avant d'utiliser l'introducteur, se référer systématiquement au mode d'emploi, aux précautions ou mises en garde contenues dans le mode d'emploi du filtre.
- Déverrouiller l'obturateur et le retirer de l'introducteur. La valve unidirectionnelle évitera tout saignement rétrograde excessif.

AVERTISSEMENT : Maintenir l'introducteur pendant le retrait de l'obturateur ou l'insertion du filtre. Le non-respect de cette recommandation risquerait d'endommager le vaisseau.

- Tout en maintenant l'introducteur pour éviter toute force excessive sur le vaisseau, insérer lentement le filtre dans l'introducteur. Un déclic se fera entendre lorsque le filtre sera verrouillé.

5. Rétraction et retrait du filtre

- Maintenir l'introducteur afin de lui apporter de la stabilité et éviter d'appliquer trop de force sur le vaisseau.
- Tout en maintenant l'introducteur, déverrouiller le dispositif de blocage à déclic et retirer doucement le filtre. Se référer aux instructions, précautions ou mises en garde contenues dans le mode d'emploi du fabricant.

ATTENTION : En cas de résistance en essayant de rétracter le filtre intra-aortique EMBOL-X dans la cartouche, redéployez le filtre puis rétractez à nouveau le filtre intra-aortique EMBOL-X. Si vous sentez toujours une résistance, laissez le filtre en place jusqu'à ce que la gaine d'introduction EMBOL-X puisse être retirée. La gaine d'introduction EMBOL-X peut être retirée lorsque le filtre EMBOL-X est inséré en suivant les techniques standards.

- Une fois le filtre retiré, replacer l'obturateur dans l'introducteur et le verrouiller en place.

6. Retrait de la gaine d'introduction

- Quand cela est approprié, desserrer les sutures et retirer la gaine d'introduction du vaisseau tout en tirant légèrement sur les sutures pour obtenir une hémostase.

MISE AU REBUT DU PRODUIT

Jeter le produit usagé conformément aux protocoles établis par l'hôpital concernant les déchets biologiques.

ASSISTANCE TECHNIQUE

Pour une assistance technique, appeler le Support Technique Edwards au numéro suivant :
En France :.....01 30 05 29 29

APPENDIX I: Embol-X Sizers Instructions for Use

Edwards Lifesciences

INSTRUCTIONS FOR USE
EDWARDS EMBOL-X - AORTIC SIZERS

Caution: Federal law (U.S.A.) restricts this device to sale by or on the order of a physician.

DESCRIPTION
The Edwards EMBOL-X aortic sizers are designed to assist physicians in determining the outer diameter of the ascending aorta using a stainless steel sizer, as provided in kits containing 8 sizes (26mm to 40mm). The aortic sizers are intended to provide a nominal measurement of the outer diameter of the aorta, for reference purposes only.

INTENDED USE/ INDICATIONS
The EMBOL-X aortic sizers are intended for use (for references purposes only) in all procedures that require measurement of the outer diameter of the aorta. Additionally, the EMBOL-X aortic sizers may provide guidance in selection of the appropriately sized EMBOL-X arterial filter. (Please refer to the instructions for use, provided with the EMBOL-X arterial filter for detailed instruction regarding its use.)

PRECAUTIONS
- The EMBOL-X aortic sizers are distributed non-sterile.
- The EMBOL-X aortic sizers must be cleaned and steam autoclave sterilized prior to use.
- Each institution should determine the cleaning and sterilization method most appropriate for that site.
- The EMBOL-X aortic sizers may be steam autoclave sterilized in the package tray provided.
- Proper surgical procedures and techniques are the responsibility of the medical professional.
- Adequate cleaning and sterilization of the EMBOL-X aortic sizers are the responsibility of the medical facility.
- The EMBOL-X aortic sizers should be visually inspected before each use. If discoloration, small dimples, or roughening of the surface (corrosion) is detected, DO NOT USE. Corroded sizers should be discarded to prevent injury to the patient.

CLEANING
- Soak all Sizers in enzymatic solution per manufacturer's instructions.
- Use a suitable cleaning brush to remove organic debris from the surface of the Sizers.
- Rinse all components with clean water.

STERILIZATION
- Sterilize the EMBOL-X aortic sizers in steam autoclave using validated procedures for sterilization prior to each use. [Flash or Wrapped Prevac: Minimum 5 minutes at 270°F or 132°C. Maximum recommended temp for the rubber mat is 138°C.]
- The EMBOL-X aortic sizers may be steam autoclave sterilized separately or as a kit.

CLINICAL USE
The EMBOL-X aortic sizers are reusable devices, intended for multiple uses. Always clean and sterilize the Aortic Sizers prior to use.

- Visually determine the outer diameter of the ascending aorta.
- Choose an aortic sizer (one of the 8 available sizes from 26mm - 40mm) which most closely represents the presumed outer diameter of the aorta.
- Place the "half circle" aortic sizer directly over the outer surface of the ascending aorta.
- The Aortic Sizer should fit easily over the aorta, without a significant gap, and without forcing the fit.

STORAGE AND HANDLING
Handle with care. The EMBOL-X aortic sizers may be stored in the tray provided, under conditions that protect against loss or damage to the devices. Furthermore, the EMBOL-X aortic sizers may be stored in a clean, dry container or in a suitable autoclave sterilization tray.

For customer service, please contact Edwards Lifesciences LLC at the address below.

For product information or questions pertaining to sales and service, please contact Edwards Lifesciences LLC directly.

Printed in the USA.

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Made in the U.S.A.

MODE D'EMPLOI
EDWARDS EMBOL-X – CALIBREURS AORTIQUES

Attention : Conformément à la loi fédérale (Etats-Unis) le droit de vendre ou de prescrire ce produit est réservé aux médecins

DESCRIPTION
Les calibreurs aortiques Edwards EMBOL-X sont conçus pour permettre aux médecins de déterminer le diamètre extérieur de l'aorte ascendante. Ces calibreurs, constitués d'acier inoxydable, sont fournis en kits de 8 dimensions (26 mm à 40 mm). Les calibreurs aortiques sont destinés à fournir une mesure nominale du diamètre extérieur de l'aorte, à titre indicatif uniquement.

Edwards Lifesciences LLC
One Edwards Way • Irvine, CA 92614-5686 • 800-424-3278 • 949-250-2500

APPENDIX J: Embol-X Filter IFU

Edwards Lifesciences

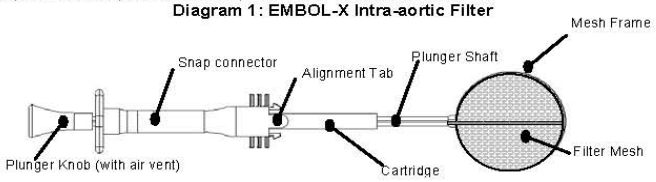
INSTRUCTIONS FOR USE
EMBOL-X INTRA-AORTIC FILTER

Caution: Federal law (U.S.A.) restricts this device to sale by, or on the order of, a physician.

1. DESCRIPTION

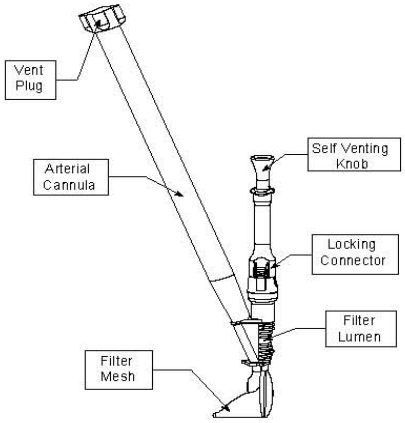
The EMBOL-X Intra-aortic Filter consists of three primary components: a distal filter or basket assembly to capture and retain particulate emboli (positioned within the aorta); a locking cartridge for introduction through the sideport of the EMBOL-X Access Device/Aortic Cannula and to ensure correct orientation of the filter during use; and a proximal syringe-like plunger mechanism to deliver and withdraw the basket into and from the aorta. The distal filter consists of a heparin-coated (Duraflo treated) mesh filter mounted on a frame.

Diagram 1: EMBOL-X Intra-aortic Filter



The EMBOL-X Intra-aortic Filter, contained in the cartridge, is inserted into the Introducer port and is deployed within the aorta by depressing its syringe-like plunger mechanism. The self-venting knob allows the air in the cartridge to automatically vent when the cartridge is inserted into the cannula and contacts blood. On deployment, the Filter opens in the lumen of the ascending aorta. The Filter is withdrawn from the aorta by pulling up on the plunger.

Diagram 2: EMBOL-X SYSTEM: EMBOL-X Intra-aortic Filter connected with EMBOL-X Access Device/Aortic Cannula



2. INDICATIONS AND INTENDED USE

The EMBOL-X Intra-aortic Filter is indicated for use with the EMBOL-X Access Device/Aortic Cannula in first time, non emergent cardiac surgery procedures requiring aortic cross clamp to capture and remove particulate emboli from the ascending aorta and heart in patients aged 18 years and older.

3. CONTRAINDICATIONS

The EMBOL-X Intra-aortic Filter is contraindicated for use in patients with:

- Aneurysm of the ascending aorta
- Aortic trauma
- Porcelain aorta

Devices with a Duraflo coating are contraindicated in patients with a known sensitivity to heparin.

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4. WARNINGS

- This device is designed, intended, and distributed for single use only. **Do not re-sterilize or reuse this device**. There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not manipulate or reposition the EMBOL-X Access Device/Aortic Cannula or the EMBOL-X Intra-aortic Filter shaft with the filter deployed. If the cannula must be repositioned, first retract the Filter. Failure to do so may cause injury to the aorta.
- Hold the base of the Introducer port of EMBOL-X Access Device/Aortic Cannula to stabilize it while inserting the EMBOL-X Intra-aortic Filter and to prevent vessel injury.
- Prior to deployment of the EMBOL-X Intra-aortic Filter, verify that the EMBOL-X Access Device is flat against the aorta and that the Filter is being deployed perpendicular to the surface of the aorta. Failure to do so may result in excessive resistance and subsequent damage to the aorta.
- Deploying the EMBOL-X Intra-aortic Filter if excessive resistance is felt may indicate improper positioning of the Access Device. Forced deployment may cause injury to the aorta.
- Failure to remove all air from the EMBOL-X Intra-aortic Filter may result in air embolism.
- The EMBOL-X Intra-aortic Filter must be retracted and removed from the EMBOL-X Access Device/Aortic Cannula prior to routine administration of protamine for heparin reversal. Failure to do so may result in thrombus formation on the Filter.
- Do not use a single EMBOL-X Intra-aortic Filter more than once. This may result in:
  - Air embolism, since the porous plug on the Filter plunger will vent only once.
  - Increased risk of thrombus formation, which may make the Filter difficult to insert or remove.
  - Distortion of the Filter frame.
- The EMBOL-X Intra-aortic Filter must be used in conjunction with the EMBOL-X Access Device/Aortic Cannula, although the EMBOL-X Access Device/Aortic Cannula may be used separately in place of a standard arterial return cannula.
- Ensure that the cross-clamp is positioned at least 2.0 cm away from the EMBOL-X Access Device/Aortic Cannula. Failure to do so may result in difficulty with insertion and/or removal of the Filter.
- Do not use a single EMBOL-X Intra-aortic Filter intra-aortically for more than **60** (sixty) minutes.
- If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X Access Device/Aortic Cannula can be removed. The EMBOL-X Access Device/Aortic Cannula can be removed with the EMBOL-X filter inserted using standard techniques.

5. PRECAUTIONS

- Supplied sterile and non-pyrogenic in undamaged package. Do not use if device shows signs of damage (i.e., cuts, kinks, crushed areas), or if package is damaged or open.
- Do not use device if the package sterile integrity appears jeopardized or is opened or damaged.
- Note "Use Before" or "Use By" date prior to use. Do not use past the allowable date.
- The EMBOL-X Intra-aortic Filter should not be used where the ascending aorta cannot be cannulated.
- The EMBOL-X Intra-aortic Filter and any other accompanying device should only be used in an operating room completely equipped for conventional cardiac surgery and by a surgeon trained in cardiac surgery.
- Proper surgical procedures and techniques are the responsibility of the medical profession. Described procedures are provided for informational purposes only. Each physician must determine the appropriate use of this device for each patient based on medical training, experience, the type of procedure employed, and the benefits and risks associated with device use.
- Dispose of used product in accordance with established hospital protocols for biohazards.
- Do not expose the device to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids. The housing may weaken or crack and subsequent use may result in patient injury.

6. OBSERVED ADVERSE EVENTS

Twelve hundred eighty-nine (1289) patients were enrolled at twenty-two (22) centers in the ICEM 2000 clinical trial for primary CABG or primary valve surgical procedures. Of these, 645 patients were randomized to the EMBOL-X Intra-aortic Filter (Treatment), and 644 patients were randomized to not receive the Aortic Filter (Control). Composite safety endpoint event rates reported during the trial are shown in Table 1.

Table 1: Composite Safety Endpoint Event Rate
Number (%)

Event	Treatment (N=645)	Control (N=644)
Limb ischemia	3 (0.5)	3 (0.5)
Gastrointestinal complications	5 (0.8)	5 (0.8)
Death	10 (1.6)	11 (1.7)
Neurologic deficit	18 (2.8)	18 (2.8)
Renal insufficiency	40 (6.2)	52 (8.1)
Myocardial infarction	67 (10.4)	64 (9.9)
Any event	110 (17.1)	122 (18.9)

OTHER ADVERSE EVENTS

The potential adverse events associated with the use of the EMBOL-X Intra-aortic Filter (as with other invasive cardiac surgery devices) include, but are not limited to, the following (in alphabetical order):

- Allergic reaction
- Angina
- ARDS
- Atrial / Ventricular arrhythmia
- Bleeding requiring transfusion
- Cardiac arrest
- Cardiac tamponade
- Coagulopathy
- Death
- Delirium
- Dissection of aortic wall
- Embolism
- Endocarditis / Pericarditis
- Endothelial disruption of aortic wall
- Gastrointestinal complications
- Heart block
- Hemothorax / Pneumothorax
- Hepatic failure
- Limb ischemia
- Metabolic coma
- Myocardial infarction
- Pneumonia
- Prolonged ventilation
- Renal insufficiency
- RIND / TIA / Stroke
- Septicemia
- Shock
- Sternal infection
- Visual impairment

7. CLINICAL STUDY

Study Design

The EMBOL-X ICEM 2000 trial was a prospective, multi-center, 1:1 randomized, controlled study to demonstrate the safety and effectiveness of the EMBOL-X Intra-aortic Filter (and the associated EMBOL-X Access Device/Aortic Cannula) in capturing particulate emboli during first-time non-emergent coronary artery bypass graft (CABG) or aortic/mitral valve repair/replacement procedures utilizing cardiopulmonary bypass. The study was conducted at 22 sites, and was comprised of 1289 randomized patients, of which 645 were randomized to the EMBOL-X Intra-aortic Filter (Treatment arm) and 644 were randomized to not receive the Aortic Filter (Control).

Primary Endpoints

The safety hypothesis was that of equivalence between a composite perioperative complication rate for patients undergoing cardiac surgery using the EMBOL-X Intra-aortic Filter (Treatment) as compared to the current CPB cardiac surgery practice of using a standard aortic cannula with no Aortic Filter (Control). The primary safety composite endpoint was comprised of the following post-operative clinical events, measured from the time of randomization (the operation) through hospital discharge or 30 days, whichever occurred first: Neurologic deficit (mild and severe); Renal insufficiency (with and without dialysis); Gastrointestinal (GI) complications; Perioperative Myocardial Infarction (MI); Limb-threatening peripheral embolism (Limb Ischemia); and Death. The primary effectiveness endpoint was the capture of one or more particulate emboli by the filter (Treatment arm only) in at least 75% of the filtered patients, with particulate debris visually confirmed by light microscopy.

Patients Studied

The patient population of this study was limited to patients undergoing first time, non-emergent Coronary Artery Bypass Grafting (CABG), aortic valve replacement or mitral valve repair or replacement only, aged 60 years and older.

Inclusion and Exclusion criteria

1. *Inclusion Criteria*

   Patients who met all of the following criteria were considered for study participation:
   - Patients who are at least 60 years of age;
   - Patients having first time non-emergent conventional (arrested heart) Coronary Artery Bypass Graft (CABG) or aortic valve replacement or mitral valve repair/replacement surgery;
   - Patients who will have CABG or valve surgery with planned median sternotomy for cardiopulmonary bypass (CPB);

2. *Exclusion Criteria*

   Patients who met any one of the following criteria were not eligible to be enrolled into the study:

   Planned Surgery - Cardiac & Neurologic
   - Patients having emergent surgery;
   - Patients undergoing a combined cardiac surgery procedure, such as CABG and valve repair / replacement;
   - Patients undergoing a double valvular surgery (e.g. aortic and mitral valve replacement);
   - Patients undergoing procedures that involve repair / replacement of the ascending aorta;
   - Patients having port access or beating heart surgery;
   - Patients undergoing an interventional carotid procedure (including endarterectomy or angioplasty) within 7 days of CABG surgery (prior to or following).

   Patient Status / History - Cardiac
   - Patient who are hemodynamically unstable (i.e., cardiogenic shock, as defined by systolic blood pressure <80 mmHg for more than 5 minutes);
   - Patients who have had previous cardiac surgery;
   - Patients who have had previous aortic reconstruction (i.e., aortic grafts, aneurysm repairs) of the ascending or arch aorta;
   - Patients with an aneurysm in the ascending aorta.

   Patient Status / History - Neurologic
   - Patients with a history of major stroke, as defined by a clinical history of fixed, focal neurological deficit attributable to stroke (i.e. ischemia of the central nervous system);
   - Patients who present with any evidence of neurologic deficit on the preoperative neurological assessment (NIH Stroke Scale), if the deficit is attributable to stroke.
   - Patients on active treatment for psychosis (e.g., major tranquilizers, Lithium).

- (Note: Patients who have had MRI or CT with evidence of stroke on imaging were included in the study, so long as there is no evidence of residual focal deficit. Additionally, patients with a history of TIA were included in the study.)

Patient Status / History - General

- Patients with renal failure that requires dialysis;
- Patients with other medical illnesses that are associated with limited life expectancy (< 1 year) following the planned procedure;
- Patients with a strong history of alcohol abuse, as defined by one or more of the following:
  - regular consumption of 5 or more drinks per day,
  - documented evidence of organ dysfunction or cirrhosis,
  - elevated PT as evidence of impaired liver function, or
  - history of blackouts, seizures or esophageal varices with or without GI bleeding
- Patients who have participated in another clinical study to evaluate a drug or device within the last 30 days.

Study Methods

An independent Clinical Events Committee, blinded to the treatment arm, adjudicated all major clinical events. Clinical follow-up for all treated patients extended to 30-days post-procedure or discharge, whichever occurred first. All randomized patients were included in the intent-to-treat analysis.

Study Results

Of the 1289 patients studied, 927 (71.9%) were male, and 1042 (80.8%) were 65 years of age or older; 376 (29.2%) were diabetic, 65 (5.0%) had a LVEF < 30%, and 388 (30.1%) had a prior MI.

Key baseline and medical history variables were generally comparable between study groups (Table 2). Logistic regression was performed which showed that the between group differences in baseline characteristics did not influence interpretation of the primary composite safety endpoint results.

Table 2: Key baseline and medical history variables

	Filter	Control	P-value
Male	72.9 %	71.0 %	0.45
Age (mean)	70.8 yr	70.8 yr	0.92
BMI < 25 kg/m2	25.1%	24.4%	0.38
LVEF ≤ 25%	4.7%	4.5%	0.89
Hypertension	78.1%	75.0%	0.18
Renal Insufficiency	2.6%	2.5%	0.86
Diabetes	28.4%	30.0%	0.53
Prior Stroke	3.3%	5.1%	0.09
Cerebrovascular Disease	4.5%	5.6%	0.37
Prior Stroke or Cerebrovascular Disease	6.7%	8.7%	0.17
Peripheral Vascular Disease	13.6%	13.5%	0.94
History of Aortic Disease	3.3%	7.1%	0.002
Atrial Fibrillation	13.3%	9.0%	0.01
Valvular Dysfunction	32.6%	27.2%	0.03
Carotid Stenosis	12.3%	8.1%	0.01

173 (13.4%) of the randomized 1289 patients underwent a valve repair or replacement procedure, while 1116 (86.6%) received a CABG procedure. Partial occlusion clamps were used in 521 (40.4%) of the cases, the mean CPB and cross clamp times for Treatment (Control) were 91.6 (88.8) and 64.3 (63.3) minutes, respectively. For the Treatment patients, the EMBOL-X Intra-aortic Filter was in place for a mean of 20.9 minutes (range of 0-59 minutes). There were no statistically significant differences between groups in surgical procedure characteristics (Table 3).

Table 3: Operative Variables

	EMBOL-X Filter (n=645) %	Control (n=644) %	*p* value
Surgery			
CABG	86.2	87.0	0.69
Valve	13.8	13.0	
Partial Clamp	40.9	39.9	0.71
Aortic Clamp Repositioned	6.4	6.7	0.82
	Mean	**Mean**	
CPB Time (min.)	91.6	88.8	0.12
Cross Clamp Time (min.)	64.3	63.3	0.57
Total Number of Grafts	2.8	2.8	0.82
Proximal Anastomosis	2.1	2.1	0.35
Filter Dwell Time (min.)	20.9	N/A	

The scheduled study follow up was to patient discharge or 30 days, whichever occurred first. Patients were followed for a median of 7.0 days (mean of 8.3 days, range of 1-30 days). The primary safety endpoint was met, where the occurrence of the composite safety endpoint was equivalent between groups (Treatment 17.1% vs. Control 18.9%, equivalency p <0.001), See Table 4). Additional, Table 4 shows there were no significant differences between groups in any of the adverse event components of the composite safety endpoint.

Table 4: Primary Composite Safety Endpoint
Number (%)

Event	Treatment (N=645)	Control (N=644)	P-Value	RR (95% CI)	Difference (95% CI)
Death	10 (1.6)	11 (1.7)	0.82	0.91 (0.39 – 2.12)	-0.002 (-0.015 – 0.012)
Neurologic deficit (Stroke/TIA)	18 (2.8)	18 (2.8)	1.00	1.00 (0.52 – 1.90)	0.000 (-0.018 – 0.018)
Stroke	17 (2.6)	14 (2.2)	0.59	1.21 (0.60 – 2.44)	0.005 (-0.012 – 0.021)
TIA	1 (0.2)	4 (0.6)	0.22	0.25 (0.03 – 2.23)	-0.005 (-0.011 – 0.002)
Renal insufficiency (RI)	40 (6.2)	52 (8.1)	0.19	0.77 (0.52 – 1.14)	-0.019 (-0.047 – 0.009)
RI (w/o dialysis)	33 (5.1)	43 (6.7)	0.23	0.77 (0.49 – 1.19)	-0.016 (-0.041 – 0.010)
RI (dialysis)	7 (1.1)	9 (1.4)	0.61	0.78 (0.29 – 2.07)	-0.003 (-0.015 – 0.009)
Myocardial infarction (MI)	67 (10.4)	64 (9.9)	0.79	1.05 (0.76 – 1.45)	0.004 (-0.028 – 0.037)
Q Wave MI	21 (3.3)	18 (2.8)	0.63	1.16 (0.63 – 2.17)	0.005 (-0.014 – 0.023)
CK-MB Elevation	46 (7.1)	46 (7.1)	0.99	1.00 (0.67 – 1.48)	0.000 (-0.028 – 0.028)
Gastrointestinal complications (GI)	5 (0.8)	5 (0.8)	1.00	1.00 (0.29 – 3.43)	0.000 (-0.010 – 0.010)
Limb ischemia	3 (0.5)	3 (0.5)	1.00	1.00 (0.20 – 4.93)	0.000 (-0.007 – 0.007)
Any event	110 (17.1)	122 (18.9)	0.38	0.90 (0.71 – 1.14)	-0.019 (-0.061 – 0.023)

Death: Death for any cause
Stroke: Central neurologic deficit persisting for > 24 hours
Transient neurologic deficit (TIA): An ischemic event of the central nervous system that causes a neurologic deficit persisting for < 24 hours
Renal insufficiency: Increase of serum creatinine to > 2.0 mg/dl or a 50% or greater increase over abnormal baseline prior to procedure
Renal insufficiency (dialysis): The new requirement for dialysis
Q-Wave MI: New pathological Q-Waves in 2 or more contiguous leads
Non Q-Wave MI: CPK > 5x normal and CK-MB > 5x above the upper limit of normal for the institution, in the absence of new Q-Waves
Gastro-Intestinal Complications: include GI bleeding requiring transfusion; Pancreatitis with abnormal amylase/lipase requiring NG suction therapy; Cholecystitis requiring cholecystectomy or drainage; Mesenteric ischemia requiring exploration
Limb-threatening Peripheral Embolism: Acute onset of diminished pulse, altered pallor (discoloration, either hypo- or hyper-), and pain as evidence of limb-threatening peripheral ischemia

No (0) aortic dissections were seen in the Filter arm and two (2) were seen in the Control arm.
18 of 22 enrolling centers performed peri-procedural ultrasound imaging (TEE or EPI), permitting fair analysis in a subset of 70.6% of the randomized patients.

Table 5: Echocardiographically Evident Endothelial Disruptions Observed through Imaging

Treatment n/N (%)	Control n/N (%)	P-Value	Difference (95% CI)
42/456 (9.2)	9/454 (2.0)	< 0.001	0.072 (0.048 – 0.097)

As shown in Table 5, there were significantly more endothelial disruptions in the Treatment group than in the Control group (9/2% vs. 2.0%). The majority of these disruptions (78%) were not observed by the surgeon and, in Table 6, the presence of an echocardiographically evident endothelial disruption did not put the patient at a greater risk for experiencing adverse events which formed the composite safety endpoint (median follow-up was 7.0 days).

Table 6: Composite Endpoint Events Stratified by Endothelial Disruptions Observed through Echocardiographic Imaging

Arm	Events in Patients With Endothelial Disruption n/N (%)	Events in Patients Without Endothelial Disruption n/N (%)	P-Value	Difference (95% CI)
Treatment	2/42 (4.8)	74/414 (17.9)	0.03	-0.131 (-0.205 – -0.057)
Control	1/9 (11.1)	81/445 (18.2)	1.0	-0.071 (-0.279 – 0.138

Although follow-up after discharge was not planned in the original study, additional follow-up was obtained by phone to investigate whether there were any clinical correlations associated with the increased occurrence of endothelial disruptions in the test arm.

Follow-up (mean 360 days, range 149-771 days) was obtained for 90.5% (430/475) of the patients at 4 high enrolling centers which did imaging and in 98% (51/52) of the patients with endothelial disruptions. For the patients with follow-up, a composite event rate of 6.1% (n=13 patients) was seen in both arms; there was no statistical correlation seen with patients where an endothelial disruption was observed. Three (3) additional aortic dissections/aneurysms were noted in the Control arm and none (0) were seen in the Filter arm in these follow up patients; resulting in a total of no (0) aortic dissections/aneurysms in the Filter arm and five (5) aortic dissections/aneurysms in the Control arm for patients entered in the clinical study.

Table 7: Composite Endpoint Events Within Various Subgroups

Subgroup	EMBOL-X Filter n/N (%)	Control n/N (%)	P	RR (95% CI)	Difference (95% CI)
Type of Surgery					
CABG	95/556 (17.1)	104/560 (18.6)	0.52	0.92 (0.71 – 1.18)	-0.015 (-0.060 – 0.030)
Valve	15/89 (16.9)	18/84 (21.4)	0.44	0.79 (0.42 – 1.46)	-0.046 (-0.163 – 0.071)
Sex					
Male	79/470 (16.8)	90/457 (19.7)	0.26	0.85 (0.65 - 1.12)	-0.029 (-0.079 – 0.021)
Female	31/177 (17.5)	32/185 (17.3)	0.96	1.01 (0.65 - 1.59)	0.002 (-0.076 – 0.080)
Age Group					
< 65	18/130 (13.9)	19/117 (16.2)	0.60	0.85 (0.47 – 1.54)	-0.024 (-0.113 – 0.065)
65 – 69	29/160 (18.1)	32/181 (17.7)	0.91	1.03 (0.65 – 1.62)	0.004 (-0.077 – 0.086)
70 – 74	23/158 (14.6)	26/152 (17.1)	0.54	0.85 (0.51 – 1.42)	-0.025 (-0.107 – 0.056)
75 – 79	26/129 (20.2)	24/121 (19.8)	0.95	1.02 (0.62 – 1.67)	0.003 (-0.096 – 0.102)
≥ 80	14/68 (20.6)	21/73 (28.8)	0.26	0.72 (0.40 – 1.29)	-0.082 (-0.224 – 0.061)
≥ 75	40/197 (20.3)	45/194 (23.2)	0.49	0.88 (0.60 – 1.28)	-0.029 (-0.111 – 0.053)
BMI					
< 25 kg/m^2	18/162 (11.1)	30/157 (19.1)	0.05	0.58 (0.34 – 1.00)	-0.080 (-0.158 – -0.001)
25-29.9 kg/m^2	55/294 (18.7)	51/288 (17.7)	0.75	1.06 (0.75 - 1.49)	0.010 (-0.053 – 0.073)
≥ 30 kg/m^2	37/191 (19.4)	41/197 (20.8)	0.72	0.93 (0.63 - 1.38)	-0.014 (-0.094 – 0.065)
LVEF					
≤ 25%	3/30 (10.0)	10/29 (34.5)	0.02	0.29 (0.09 - 0.95)	-0.245 (-0.456 – -0.033)
> 25%	106/615 (17.2)	112/613 (18.3)	0.64	0.94 (0.74 - 1.20)	-0.010 (-0.053 – 0.032)
Plaque					
Present	12/82 (14.6)	18/93 (19.4)	0.41	0.76 (0.39 – 1.47)	-0.047 (-0.159 – 0.065)
Absent	59/350 (16.9)	57/342 (16.7)	0.95	1.01 (0.73 – 1.41)	0.002 (-0.054 – 0.058)
Not Evaluable	39/213 (18.3)	47/209 (22.5)	0.29	0.81 (0.56 – 1.19)	-0.042 (-0.119 – 0.035)
Hypertension					
Yes	87/504 (17.3)	102/483 (21.1)	0.12	0.82 (0.63 – 1.06)	-0.039 (-0.088 – 0.011)
No	23/141 (16.3)	20/161 (12.4)	0.33	1.31 (0.75 – 2.29)	0.039 (-0.040 – 0.118)
Renal Insufficiency					
Yes	6/17 (35.3)	10/16 (62.5)	0.12	0.56 (0.27 – 1.19)	-0.272 (-0.613 – 0.069)
No	104/628 (16.6)	112/628 (17.8)	0.55	0.93 (0.73 – 1.18)	-0.013 (-0.054 – 0.029)
Diabetes					
Yes	42/183 (23.0)	37/193 (19.2)	0.37	1.20 (0.81 – 1.77)	0.038 (-0.045 – 0.120)
No	68/462 (14.7)	85/451 (18.9)	0.10	0.78 (0.58 – 1.05)	-0.041 (-0.090 – 0.007)
Prior Stroke					
Yes	2/21 (9.5)	7/33 (21.2)	0.46	0.45 (0.10 – 1.96)	-0.117 (-0.321 – 0.087)
No	108/624 (17.3)	115/611 (18.8)	0.49	0.92 (0.73 – 1.17)	-0.015 (-0.058 – 0.028)
Cerebrovascular Disease					
Yes	5/30 (16.7)	14/35 (40.0)	0.04	0.42 (0.17 – 1.02)	-0.233 (-0.455 – -0.012)
No	105/617 (17.0)	108/607 (17.8)	0.72	0.96 (0.75 – 1.22)	-0.008 (-0.050 – 0.035)
Prior Stroke or Cerebrovascular Disease					
Yes	6/43 (14.0)	17/56 (30.4)	0.06	0.46 (0.20 – 1.07)	-0.164 (-0.332 – 0.004)
No	104/602 (17.3)	105/588 (17.9)	0.79	0.97 (0.76 – 1.24)	-0.006 (-0.049 – 0.037)
Peripheral Vascular Disease					
Yes	21/88 (23.9)	26/87 (29.9)	0.37	0.80 (0.49 – 1.31)	-0.060 (-0.192 – 0.071)
No	89/557 (16.0)	96/557 (17.2)	0.57	0.93 (0.71 – 1.21)	-0.013 (-0.056 – 0.031)
COPD					
Yes	19/82 (23.2)	17/87 (19.5)	0.56	1.19 (0.66 – 2.12)	0.036 (-0.087 – 0.160)
No	91/565 (16.1)	105/555 (18.9)	0.22	0.85 (0.66 – 1.10)	-0.028 (-0.073 – 0.016)
Vent. Arrhythmia					
Yes	8/41 (19.5)	11/29 (37.9)	0.09	0.51 (0.24 – 1.12)	-0.184 (-0.396 – 0.027)
No	102/606 (16.8)	111/613 (18.1)	0.56	0.93 (0.73 – 1.19)	-0.013 (-0.055 – 0.030)

The primary efficacy endpoint was met, where 96.8% of the filters deployed were shown to have captured at least one particulate embolus; and the histologic composition of these particulates were identified (Tables 8 and 9).

Table 8: Summary of Particulate Capture Effectiveness

Attribute	Result
Number EMBOL-X Filters Deployed	618
Number (%) Filters Which Captured ≥ 1 Particle	598 (96.8%)
Lower 95% Confidence Bound on Percent of Filters Which Captured ≥ 1 Particle	95.3%

Table 9: Captured Particulate Histology[1]

Percent (*n*)

Histological description (N= 623 Filter Treatment Cases)[1,2]	Randomized CABG and Valve (n=623)	Randomized CABG (n=538)	Randomized Valve (n=85)
Total Dissolved/No emboli	24.4 (152)	24.2 (130)	25.9 (22)
Total Filters for Histological Analysis	75.6 (471)	75.8 (408)	74.1 (63)
Fibrous Atheroma	86.6 (408)	87.0 (355)	84.1 (53)
Fibrocalcific Atheroma	3.4 (16)	1.0 (4)	19.0 (12)
Grumous atheroma / cholesterol	1.3 (6)	1.5 (6)	0 (0)
Medial tissue	0.6 (3)	0.7 (3)	0 (0)
Fibrofatty/Adventitial tissue	1.7 (8)	1.0 (4)	6.3 (4)
Platelets/Fibrin	37.8 (178)	37.0 (151)	42.9 (27)
True RBC thrombus/Clot	2.1 (10)	2.0 (8)	3.2 (2)
Displaced or dissolved (during processing) [2]	21.0 (131)	20.6 (111)	23.5 (20)
No particulate emboli observed	3.4 (21)	3.5 (19)	2.4 (2)
Particulate Capture Rate per Filter	96.6 (602)	96. 5 (519)	97.6 (83)

1 Totals may not equal 100% due to multiple particulates within the same Filter.
2 Filters with dissolved and 0 samples not included in percentage calculations of histologic composition.

Figure 1 presents the distribution of the number of particulates captured. A mean of 5.6 particulates were captured by the EMBOL-X Filter with a range of 0- 25 particulates. The mean surface area was 3.8 sq mm with a range of 0-69.9 sq mm. This information is further illustrated in Tables 10 and 11 which summarize the distribution of the number of particulates captured and the mean surface area of the particulates captured.

Figure 1. Particle Number Distribution

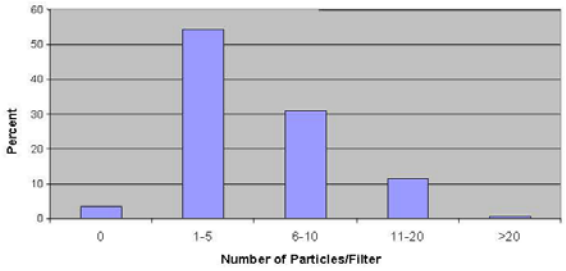

Table 10: Summary of Numbers of Particles Captured Per Filter

Number of Particles Captured	CABG (N=538) N (%)	Valve (N=85) n (%)	All Randomized (N=623) n (%)
0	19 (3.5)	2 (2.4)	21 (3.4)
1-5	299 (55.6)	39 (45.9)	338 (54.3)
6-10	158 (29.4)	33 (38.8)	191 (30.7)
11-20	59 (11.0)	11 (12.9)	70 (11.2)
>20	3 (0.6)	0 (0.0)	3 (0.5)
Mean	5.6	6.2	5.6
Median	5	6	5
Range	0 - 25	0 - 19	0 - 25

Table 11: Summary of Total Surface Area of All Particles Caught Per Filter

Surface Area Summary Statistics	CABG (N=536) [1]	Valve (N=85)	All Randomized (N=621)
Mean (mm^2)	3.7	4.0	3.8
Median (mm^2)	2.1	2.2	2.1
Range (mm^2)	0 – 69.9	0 - 31.1	0 - 69.9

[1]Excludes 2 filters (2-randomized/CABG). Although the filters had visible particles seen in them based on gross histology, the surface areas could not be measured.

Conclusions
The primary safety endpoint was met, with the EMBOL-X Intra-aortic Filter arm composite event rate statistically equivalent to that of standard treatment (17.1% vs. 18.9%, p<0.001). In addition, differences in the stratified events between the filter and non-filter groups were not statistically different. The primary effectiveness endpoint was also met, with particulate emboli capture demonstrated in 96.8% of all filters analyzed (p<0.001). Therefore, the data shows that the EMBOL-X Intra-aortic Filter safety profile was equivalent to that of the current standard treatment of standard cannulation without filtration, and the Filter was effective in capturing particulates.

The composite safety event rate and the adverse event components which comprise it cited reflect experience gained under closely monitored conditions of a clinical trial in a selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

8. RESULTS FROM THE EUROPEAN CLINICAL REGISTRY

European Registry
Data to support additional cardiac surgery indications for the EMBOL-X Intra-aortic Filter were obtained from the post market European ICEM Registry of 1645 patients. Seventeen (17) centers in Europe enrolled patients in this prospective, consecutive enrollment registry.

Registry Patient Demographics
Since this was a post market registry, the determination of the type of patients on whom to use an EMBOL-X Aortic Filter was the individual surgeon's decision. However, each center was required to enroll into the Registry each and every patient where the EMBOL-X Filter device was used. There was no suggestion by EMBOL-X as to the criteria for patient selection, although patient selection criteria were captured in the case report forms.

The patient population of the Registry included the following patients: those undergoing combination CABG and valve surgery (14.9%); those who had prior CABG or valve surgery (4.7%); those undergoing emergent cardiac surgery (1.5%); other cardiac surgery (eg. Myxoma excision, 2.7%) and patients less than 60 years old (20.7%). In addition, there were a significant number of European Registry patients who met the criteria for the US IDE Clinical Study or patients undergoing first time, non-emergent coronary artery bypass grafting (CABG), aortic valve replacement or mitral valve repair or replacement only, aged 60 years and older (51.9%). Patient Demographics and Operative Details are shown in Table 12.

Table 12. Demographic and Operative Summary

	All Registry patients (N=1645)	IDE Eligible Registry patients (N=828)
Age (yr): mean (range), n	67.1 (11[1] – 89) 1601	71.0 (60 – 88) 828
Weight (kg): mean (range), n	77.3 (36 – 177) 1570	76.7 (36 – 165) 819
Sex		
Males: n/N (%)	1118/1587 (70.4%)	564/820 (68.8%)
Females: n/N (%)	469/1587 (29.6%)	256/820 (31.2%)
NYHA Class		
1 or 2: n/N (%)	435/1400 (31.1%)	221/740 (29.9%)
3 or 4: n/N (%)	965/1400 (68.9%)	519/740 (70.1%)
Aortic cross clamp time (min.): mean (range), n	66.9 (10 – 205) 877	61.8 (20 – 183) 483
Filter insertion time (min): mean (range), n	32.9 (0.3 – 187) 1513	32.3 (2 – 187) 794
Number Proximal Anastomoses: mean (range), n	1.6 (0 – 7) 1275	1.7 (0 – 5) 696
Operation		
CABG: % (n/N)	63.9%[2] (1004/1572)	80.4% (666/828)
Valve: % (n/N)	17.7%[2] (278/1572)	19.6% (162/828)
CABG/Valve: % (n/N)	15.6% (245/1572)	0.0% (0)
Other: % (n/N)	2.9% (45/1572)	0.0% (0)

1 This was the only patient below the age of 18, this patient weighed 43.6 kg.
2 Includes patients with prior CABG or valve surgery for all Registry patients.

Registry Results

For the demonstration of patient safety, the clinical results from the European Registry were compared to the Filter arm of the US IDE study, both for the Registry as a whole and within each cardiac surgery procedural subgroup. The European Registry patient population was compared to the Filter Arm of the US IDE Study through analyses of the Composite Safety endpoint as defined in the US IDE Study (See Section 7). The Composite Safety Endpoint was comprised of the following post-operative clinical events: Neurologic deficit (mild and severe); Renal insufficiency (with and without dialysis); Gastrointestinal (GI) complications; Perioperative Myocardial Infarction (MI); Limb-threatening peripheral embolism (Limb Ischemia); and Death.

There were no increases in the composite safety endpoint between the IDE Eligible Registry patients and the Non-IDE Eligible Registry patients, who were combination CABG/valve or reoperations. Patients undergoing emergent cardiac surgery had higher event rates and patients < 60 yrs had lower event rates; both results were expected given the preoperative risk factors. Further adjustments for preoperative risk factors when compared to a published, validated univariate analyses of morbidity indicated that the observed odds ratio was less than expected. Similarly, analyses of mortality and preoperative patient risk factors indicate that the observed mortality was comparable to the expected mortality rate seen in the European Registry patients.

The following table summarizes the results of the European ICEM Registry.

Table 13. Composite Events Among Registry patients Outside IDE Study Entry Criteria Compared to IDE Eligible Registry patients and the US IDE Filter Study Arm

Event	Prior Surgery (N=74)[1] n (%)	Combination or Other Surgery (N=277)[1] n (%)	Emergent Surgery (N=24)[1] n (%)	<60 Years of Age (N=318)[1] n (%)	IDE Eligible Registry (N=799) n (%)	US IDE Study Filter Arm (N=645) n (%)
Death	4 (5.4%)	11 (4.0%)	6 (25.0%)	5 (1.6%)	27 (3.4%)	10 (1.6%)
Neurologic Deficit (Stroke/TIA)	3 (4.1%)	7 (2.5%)	1 (4.2%)	4 (1.3%)	18 (2.3%)	18 (2.8%)
Stroke	3 (4.1%)	4 (1.4%)	1 (4.2%)	2 (0.6%)	13 (1.6%)	17 (2.6%)
TIA	0 (0.0%)	3 (1.1%)	0 (0.0%)	2 (0.6%)	5 (0.6%)	1 (0.2%)
Renal Insufficiency	1 (1.4%)	14 (5.1%)	3 (12.5%)	7 (2.2%)	28 (3.5%)	40 (6.2%)
w/o dialysis	0 (0.0%)	8 (2.9%)	0 (0.0%)	1 (0.3%)	11 (1.4%)	33 (5.1%)
Dialysis	1 (1.4%)	6 (2.2%)	3 (12.5%)	6 (1.9%)	17 (2.1%)	7 (1.1%)
Q-Wave Myocardial Infarction	2 (2.7%)	6 (2.2%)	2 (8.3%)	7 (2.2%)	21 (2.6%)	21 (3.3%)
GI Complication	0 (0.0%)	1 (0.4%)	1 (4.2%)	1 (0.3%)	10 (1.3%)	5 (0.8%)
Limb Ischemia	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (0.3%)	2 (0.3%)	3 (0.5%)
Any Event	8 (10.8%)	29 (10.5%)	7 (29.2%)	19 (6.0%)	75 (9.4%)	71 (11.0%)

1 Patients may belong to more than one of these categories, i.e., the categories are not mutually exclusive.
Clinical Event rates as defined in the US IDE Study (see Table 4)

A total of 98.2% of the EMBOL-X® Aortic Filters used in the Registry captured one or more particulates (1541 of the 1569 Aortic Filters and a lower one-sided 95% confidence bound of 97.6%). This is comparable to the US IDE Study, where 96.8% of the EMBOL-X Aortic Filters captured one or more particulates. The median number of particulates captured per filter was 7 particulates/filter (mean of 8.5 particulates/filter) and the median total surface area was 3.8 mm2 per filter (mean of 6.6 mm2).

Conclusions from the European Registry

The results of this post market European Registry demonstrate the safety of the EMBOL-X Intra-aortic Filter in patients in the cardiac surgery populations of: patients who had prior CABG or valve surgery, combination CABG/valve surgery, emergent surgery, and adult patients less than 60 years of age. This data supports the proposed indication to use of the EMBOL-X Intra-aortic Filter in the broader cardiac surgery population or in cardiac surgery procedures to capture and remove particulate emboli from the ascending aorta and heart during and following cross clamp removal in patients aged 18 years and older.

9. METHOD OF USE

I. Materials Required

- Container of sterile normal saline solution for wetting the filter prior to use.
- EMBOL-X Access Device/Aortic Cannula for vascular access to the aorta.
- EMBOL-X Aortic Sizers.

II. Inspection Prior to Use

Visually examine the following:

- The package integrity. If the package sterile integrity appears to have been jeopardized, do not use.
- Remove the EMBOL-X Intra-aortic Filter from the package and inspect to ensure that it has not been damaged or has components missing. If the device appears damaged or has components missing, do not use.
- The Filter's vent knob, a built in self-venting plug for exposures to any fluids. This would prevent the plug from venting air properly. The plug is only able to vent air once and will stop venting once fluids contact it. If the vent plug appears to have contacted fluids prior to Filter insertion, do not use.

III. Preparation for Use

- Verify that there are no aneurysmal changes or trauma present in the ascending aorta, visually or with epiaortic imaging, if used.
- Choose an EMBOL-X Aortic Sizer which most closely represents the size of the aorta. Using the Sizer, measure the outer diameter (OD) of the aorta.
- Once the outer diameter has been established, estimate the wall thickness of the aorta. The inner diameter (ID) of the aorta is estimated by subtracting twice the wall thickness from the outer diameter of the aorta [ID = OD – (2x wall thickness)]. Select the appropriate sized EMBOL-X Intra-aortic Filter based on the aortic inner diameter (refer to Table 12, below).

- Maintaining the Filter cartridge in an upright position, thoroughly moisten the EMBOL-X Intra-aortic Filter by submerging the distal Filter end in a container of sterile saline and slowly swirling it around the container. This is intended to remove all air from the Filter material. Do not submerge the Filter plunger knob as this will prevent it from venting properly once the Filter is inserted.
- Retract the EMBOL-X Intra-aortic Filter fully into the cartridge while gently pinching the edges of the Filter between your thumb and forefinger and guiding the edges of the Filter upwards.

WARNING: Do not use a single EMBOL-X Intra-aortic Filter more than once. This may result in:
- Air embolism, since the porous plug on the Filter plunger will vent only once;
- Increased risk of thrombus formation, which may make the Filter difficult to insert and remove; or
- Distortion of the Filter frame.

WARNING: Failure to remove all air from the EMBOL-X Intra-aortic Filter may result in air embolism.

Table 12: EMBOL-X Intra-aortic Filter Sizes and Aortic Internal Diameters.

Filter Sizes	Minimum Aortic Inner Diameter (mm)	Maximum Aortic Inner Diameter (mm)
X-Small (26mm)	22 mm	26 mm
Small (29 mm)	26 mm	29 mm
Medium (32 mm)	29 mm	32 mm
Large (34 mm)	32 mm	35 mm
X-Large (37 mm)	35 mm	40 mm

IV. Insertion and Deployment of the EMBOLX Intra-aortic Filter

- In order to capture emboli liberated upon the application of the aortic cross clamp, prepare to deploy an EMBOL-X Intra-aortic Filter.
- In order to capture emboli liberated upon the removal of the aortic cross clamp, prepare to deploy an EMBOL-X Intra-aortic Filter.
- While holding the base of the cannula component to prevent excessive force on the aorta, unlock the obturator and remove it from the introducer port of the EMBOL-X Access Device. The one-way valve will prevent excessive backbleeding.
- While still holding the cannula, slowly insert the EMBOL-X Intra-aortic Filter (retracted into cartridge) into the introducer port until an audible "click" is heard. The EMBOL-X Intra-aortic Filter is now locked in place.
- Confirm de-airing of the Filter and cartridge by looking for blood in the knob of the plunger. If blood is not visible in the knob, DO NOT DEPLOY the filter. Remove the Filter and insert a new one.
- Verify that the suture flange of the Access Device is flat on the aorta and that the filter is perpendicular to the aorta.
- Deploy the EMBOL-X Intra-aortic Filter by slowly pushing the plunger all the way down.
- If resistance is met during deployment and the Filter will not deploy, ensure that the EMBOL-X Access Device/Aortic Cannula is positioned so that the introducer port is perpendicular to the aorta prior to attempting to re-deploy the Filter If resistance is still felt, retract Filter and replace with another EMBOL-X Intra-aortic Filter.
- A partial occlusion clamp may be applied and removed while the filter in place. Remove the partial occlusion clamp prior to EMBOL-X Intra-aortic Filter removal.
- The EMBOL-X Intra-aortic Filter may be deployed for up to 60 minutes to collect any emboli that may result from the clamping procedure, intracardiac debris, or manipulation of the ascending aorta and heart during CPB surgery.

WARNING: Although the EMBOL-X Access Device/Aortic Cannula may be used separately in place of a standard arterial return cannula, the EMBOL-X Intra-aortic Filter must be used in conjunction with the EMBOL-X Access Device/Aortic Cannula.

WARNING: Hold the base of the Introducer port of EMBOL-X Access Device/Aortic Cannula while inserting the EMBOL-X Aortic Filter. Failure to do so may cause injury to the aorta.

WARNING: Do not deploy the EMBOL-X Intra-aortic Filter if excessive resistance is felt. Attempting to deploy the EMBOL-X Intra-aortic Filter when resistance is felt may indicate improper positioning of the cannula. Forcing deployment may cause injury to the aorta.

WARNING: Do not manipulate or reposition the EMBOL-X Access Device/Aortic Cannula or EMBOL-X Intra-aortic Filter shaft with the Filter deployed. If the cannula component must be repositioned, first retract the Filter. Failure to do so may cause injury to the aorta.

WARNING: Do not use a single EMBOL-X Intra-aortic Filter intra-aortically for more than **60** (sixty) minutes.

WARNING: The EMBOL-X Intra-aortic Filter must be retracted and removed from the Introducer port of the EMBOL-X Access Device/Aortic Cannula prior to routine administration of protamine for heparin reversal, since the Filter is heparin-coated. Failure to do so may result in thrombus formation on the Filter.

WARNING: Ensure that the cross-clamp is positioned at least 2.0 cm away from the EMBOL-X Access Device/Aortic Cannula. Failure to do so may result in difficulty with insertion and/or removal of the Filter.

V. EMBOL-X Intra-aortic Filter Removal

- Hold the shaft of the filter to stabilize the device and fully retract the EMBOL-X Intra-aortic Filter into the cartridge by retracting the plunger until it stops.
- Unlock and remove the EMBOL-X Intra-aortic Filter by pinching the locking connector tabs together and slowly sliding the Filter out of the introducer port.

> **WARNING**: If resistance is felt while trying to retract the EMBOL-X intra-aortic filter into the cartridge, redeploy the filter and then retract the EMBOL-X intra-aortic filter again. If additional resistance is felt, leave the filter in place until the EMBOL-X Access Device/Aortic Cannula can be removed. The EMBOL-X Access Device/Aortic Cannula can be removed with the EMBOL-X filter inserted using standard techniques.

10. PHYSICIAN TRAINING

As a means to augment proper technique, Edwards Lifesciences LLC will, upon request, provide the following training elements as needed to new centers intending to utilize the EMBOL-X Intra-aortic Filter:

- In-Service: Edwards Lifesciences LLC representative will review the method of use and present procedural and case review materials prior to first clinical use;
- Case support: Edwards Lifesciences LLC representative will support the first case;

11. HOW SUPPLIED

STERILE: The device is provided STERILE and NON-PYROGENIC when in unopened, undamaged packaging. The device is sterilized by Gamma Radiation.

CONTENTS: The EMBOL-X Intra-aortic Filter is individually packaged.

STORAGE AND HANDLING: Store sterile packaged device in a cool, dry, dark place until ready for use. Do not expose to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids.

12. ADDITIONAL INFORMATION

For product information or questions pertaining to sales and service, please contact the representative in your area or Edwards Lifesciences LLC directly.

United States/Canada

Edwards Lifesciences LLC
Irvine, CA 92614-5686

Telephone: 949-250-2500 & 800-453-8432

DISCLAIMER OF WARRANTY
EDWARDS LIFESCIENCES MAKES NO EXPRESS OR IMPLIED WARRANTY WITH RESPECT TO THE PRODUCT(S) SOLD HEREUNDER, INCLUDING ANY IMPLIED WARRANTY OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, WHICH WARRANTIES ARE EXPRESSELY DISCLAIMED. TO THE EXTENT THAT ANY PRODUCT DESCRIPTIONS AND/OR SPECIFICATIONS ARE SET FORTH HEREIN, SAID SPECIFICATIONS AND/OR DESCRIPTIONS ARE INTENDED ONLY AS GENERAL LANGUAGE AND DO NOT CONSTITUTE AN EXPRESS WARRANTY THAT THE PRODUCT SHALL CONFORM TO THE DESCRIPTION AND/OR SPECIFICATION OF THE PRODUCT.

Made in USA

Edwards, Edwards Lifesciences, the stylized E logo, EMBOL-X, and Duraflo are trademarks of Edwards Lifesciences Corporation.

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ID	LOT					STERILE R		#		Rx Only	REF
Inner Diameter	Lot Number	Consult Instructions for Use	Use By Date	Caution	Non-Pyrogenic	Gamma Sterilized	Single Use Only	Quantity	Do not use if package is damaged	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician	Catalogue Number

Appendix K: CardioGard Emboli Protection Cannula IFU

CARDIOGARD

Instructions for use

CardioGard Emboli Protection Cannula

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician.

Description

CardioGard Emboli Protection Cannula is a specially designed arterial (aortic) cannula used to remove embolic material from the aortic arch throughout the duration of the cardiopulmonary bypass procedure.

The cannula is comprised of a double lumen where the primary lumen provides oxygenated blood from the heart-lung machine to the patient and the secondary lumen performs suction of blood and embolic matter from the surgical field back to the cardiopulmonary bypass machine for filtration.

The CardioGard Emboli Protection Cannula is a 24 French aortic cannula which terminates in connecter acceptances of 3/8" (9.5mm) and 1/4" (6.3mm). The 3/8" channel provides the oxygenated blood from the CPB and the 1/4" channel is used for the suction of embolic matter.

The flow rates through the lumens of the cannula are carefully controlled so that the majority of emboli are removed by the cannula while providing net flow of blood into the aorta that is physiologically acceptable.

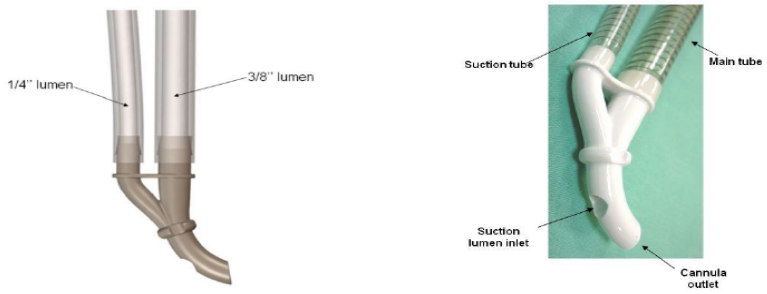

Diagram 1: The CardioGard Emboli Protection Cannula

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CARDIOGARD

Each CardioGard Emboli Protection Cannula is packaged EtO sterile and non-pyrogenic in a sealed, peel-type pouch.

Indications for use

CardioGard Emboli Protection Cannula combines the function of a standard arterial cannula with an added suction mechanism to capture debris that may result from cardiac surgery.
The CardioGard Emboli Protection Cannula is intended for perfusion of the ascending aorta during short term (<6 hours) cardiopulmonary bypass (CPB) procedures. The CardioGard suction lumen is intended for the removal of particulate emboli during surgical procedures that require CPB.

Contraindications for use

- Porcelain aorta
- Aortic trauma
- Patients with a known sensitivity to heparin.

This device is not intended for use other than as indicated and should not be used when any physical impairment would contraindicate its use.

Warnings

- The device is designed, intended, and distributed for single use only. **Do not re-sterilize or reuse this device.** There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing. In the case of product's reuse, the device might not function and cause damage to the patient.
- Do not use the CardioGard Emboli Protection Cannula without passing the necessary training (CardioGard Cannula Training- CLN0024, Rev.04).
- Always connect the 3/8" tubing to the pump linkage which delivers blood to the patient and the 1/4" tubing to the pump linkage which extracts blood from the patient.

CARDIOGARD

- In the case of an occlusion in the suction lumen, stop suction activity immediately and reduce the perfusion flow to maintain the appropriate net blood flow to the patient.
- Assure the net flow of blood to the patient body is physiologically acceptable. The blood flow drawn away from the body using the suction line must be returned to the patient by increasing the blood flow in the main line.
- Ensure that no air is trapped in the perfusion circuit while connecting the CardioGard Emboli Protection Cannula to the CPB machine.
- Increase suction flow rate gradually.
- Do not exceed the maximum suction pressure limit of 1.5 l/min.
- Anticoagulation should be routinely monitored during all CPB procedures.
- Use extreme caution when inserting the cannula if there is a possibility of tissue dissection of the aorta.
- Do not use if the device shows signs of damage, e.g., cuts, kinks, crushed areas or other signs of potential leakage.
- Do not use if the device packaging appears to be damaged or if the sterile barrier may be compromised, e.g., torn or open sterile packaging.
- Use stay-straps to protect against tubing slippage on the user-assembled connections.
- Securely tie-band the 1/4" connector to the 1/4" tube of the cannula junction prior to initiating bypass.

Precautions

- Notice the cannula creates a small change in the surgical field of view.
- Note the "Use By" date prior to use. Do not use past the allowable date.
- Dispose of used product in accordance with established hospital protocols of biohazards.
- Proper surgical procedures and techniques are the responsibility of the medical profession. Described procedures are provided for

CARDIOGARD

informational purposes only. Each physician must determine the appropriate use of the device for each patient based on medical training, experience, the type of procedure employed, and the benefits and risks associated with device use.

Complications

Possible adverse effects include, but are not limited to, the following:

- Death
- Cardiac Failure
- Stroke
- Aortic dissection or perforation
- Arterial thrombosis
- Plaque embolization
- Arrhythmia
- Excessive blood loss
- Wound infection, sepsis
- Allergic reaction to cannula materials
- Flow obstruction in the main hole of the cannula
- Flow obstruction in the suction hole of the cannula

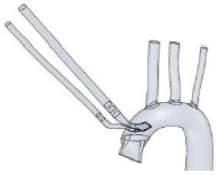
Directions for use

The CardioGard Emboli Protection Cannula is intended for use in an operating room completely equipped for conventional cardiac surgery and by a surgeon trained in cardiac surgery.

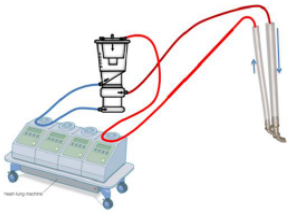
Sections 1 to 5 are the same as in the conventional cannula.

1. Prior to use, visually examine the CardioGard Emboli Protection Cannula to verify it has not been damaged. If the device appears damaged, do not use.
2. Using standard surgical technique, place the cannula similar to regular aortic cannulas.
3. Assure the cannula is in the correct direction. The cannula main perfusion tube needs to be towards the aortic arch.

CARDIOGARD



4. Secure cannula in place as done routinely. Remove the main tube cap.
5. Connect the perfusion channel to the heart lung machine in the regular location, vent the blood using regular surgical technique and secure all line connections.
6. Replace the suction tubing plugging with a clamp. Vent the blood from the suction tubing. Assure there is no air in the suction tubing.



7. Connect the suction tubing to one of the heart lung machine venting tubes using a 1/4"-1/4" connector.
8. After the initiation of bypass, adjust the appropriate net flow to the patient by increasing the blood flow in the main line in the amount of blood drawn from the body in the suction line. You can use Table 1 below in order to find the flow rate parameters that will safely support various patient body surface areas (BSA).
9. The suction can be used throughout the duration of the procedure, for example, maintaining a constant suction of 1 l/min. At the surgeon's discretion, the suction may be increased during periods of aortic manipulation or decreased during other periods when the likelihood of embolic particles is lower. When adjusting the suction flow, be sure to also adjust the forward flow in the main line to maintain appropriate net flow to the patient.
10. Observe the suction lumen throughout the surgery for signs of blockage.

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11. Upon completion of procedure, stop forward and suction flow.
12. Remove the cannula and close aortotomy using the purse string suture according to routine technique.

BSA (m^2)	Outlet Aortic Lumen Flow (l/min)	Maximum Suction Lumen Flow Rate (l/min)	Net Aortic/Perfusion Flow Rate (l/min)
1	3.9	1.5	2.4
1.1	4.1	1.5	2.6
1.2	4.4	1.5	2.9
1.3	4.6	1.5	3.1
1.4	4.9	1.5	3.4
1.5	5.1	1.5	3.6
1.6	5.3	1.5	3.8
1.7	5.6	1.5	4.1
1.8	5.8	1.5	4.3
1.9	6.0	1.4	4.6
2.0	6.0	1.2	4.8
2.1	6.0	1.1	5.1
2.2	6.0	0.7	5.3
2.3	6.0	0.5	5.5
2.4	6.0	0.2	5.8
2.5	6.0	0	6.0

Table 1: Patient's BSA and Flow rates

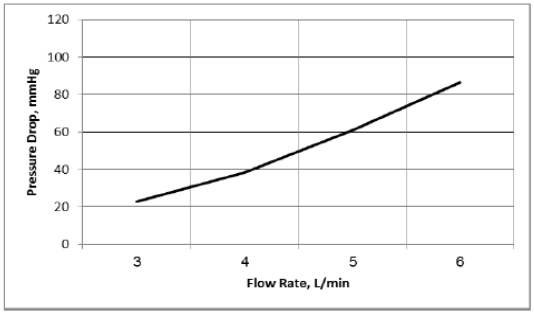

Diagram 2: Pressure Drop across CardioGard Emboli Protection Cannula

Storage and handling

Store in a controlled environment, not exceeding 40°C (104°F). Do not expose to organic solvents, ionizing radiation, ultraviolet light, or alcohol-based fluids.

CARDIOGARD

For customer service, please contact CardioGard Medical at the address below.

This product, and the use thereof, is covered by U.S. patent No. 8,523,757 and other patents pending.

REF	Catalogue number	LOT	Batch Code
	Caution, consult accompanying documents		Do not re-use
STERILE EO	Sterilized using ethylene oxide		Do not use if package is damaged
	Use by		Manufacturer
EC REP	Authorized Representative in the European community	Rx only	CAUTION: US Federal Law restricts this device to prescription only

Manufacturer:
CardioGard Medical
6 Yoni Netanyahu Street,
Or Yehuda 6037604, ISRAEL
Telephone: +972-3-5467163
Fax: +972-3-6349910

Authorized Representative:
MEDNET GmbH
Borkstrasse 10, 48163 Munster, Germany
Telephone: +49-251-32266-34
Fax: +49-251-32266-22

Revision date: March 12, 2015

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APPENDIX L: Epi-Aortic Scanning Acquisition Protocol

CTSN Epiaortic Ultrasonographic Image Acquisition Protocol (Pre and Post Procedure)

For epiaortic ultrasonographic examination, a minimal 5 views for the evaluation of the ascending aorta from the sinotubular junction to the origin of the innominate artery, and the aortic arch are required. With digital archiving, at least 3 - 5 cardiac cycles video loops are required for each view.

1. Long axis (LAX) view of ascending aorta: including visualization of the proximal, mid and distal segments should be acquired.

2. Short axis (SAX) view of ascending aorta: The ultrasound probe is positioned on the ascending aorta as proximally as possible, with the orientation marker directed toward the patient's left shoulder. Imaging plane should be perpendicular to the aorta and try to center the aorta within the imaging plane. Slowly advance the probe from the proximal ascending aorta to the mid ascending aorta and finally to the distal ascending aorta.

(1). Proximal level
(2). Mid-level
(3). Distal level

3. LAX view of proximal aortic arch: a view including visualization of the origin of the innominate artery and proximal aortic arch.

4. Additional views demonstrating significant pathology may be warranted as indicated by presence of disease.

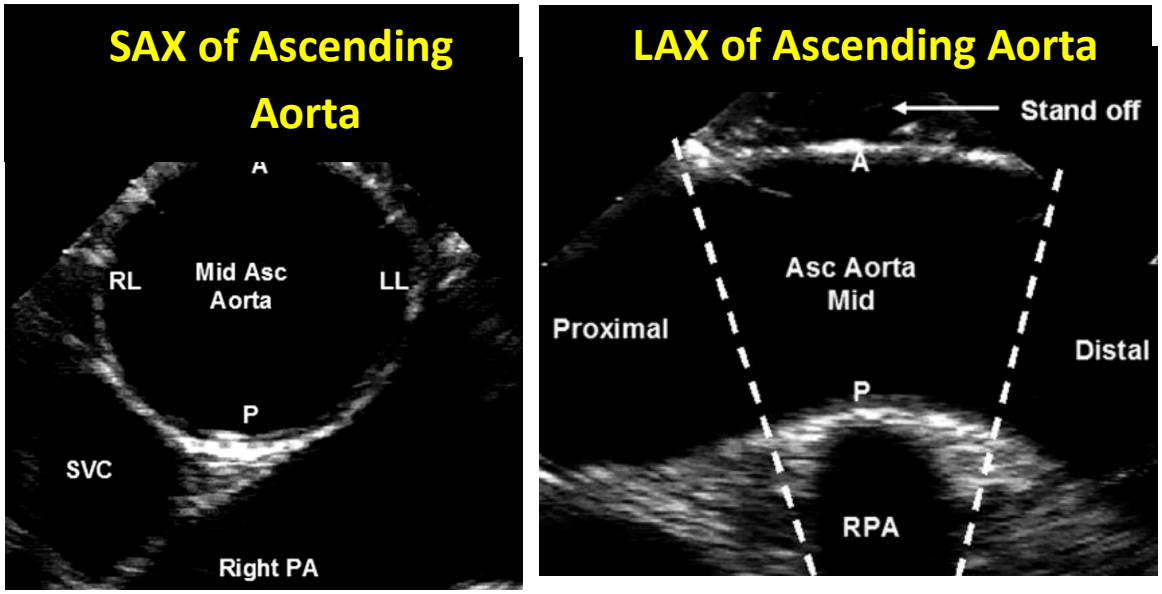

Figure 1 Short axis view of ascending aorta (left) and long axis view of ascending aorta (right) by epiaortic scanning (Adapted from J Am Soc Echocardiogr. 2007;20(11):1230).

Measurements/Data analysis

Assessment of atheroma for each of the three ascending aortic SAX segments and for the aortic arch will be performed by Katz's grade (Table). In addition, maximal plaque thickness for each segment will be measured and location of the maximal plaque within the ascending aorta will be documented.

Table 1 Grading of atheroma according to the Katz's grade (I-V)

Grades	Description of grades
I	Normal to mild intimal thickening
II	Severe intimal thickening without protruding atheroma
III	Atheroma protruding<5 mm into the aorta lumen
IV	Atheroma protruding ≥ 5 mm into the aorta lumen
V	Any thickness with mobile component

Adapted from J Am Soc Echocardiogr. 2007;20(11):1233

APPENDIX M: Treating Physician Contact Information Form

NEUROPROTECTION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT

TREATING PHYSICIAN CONTACT INFORMATION FORM

The contact information provided on this form will be used to notify your clinical site of incidental findings found on the research DWI MRI scan.

Site Name: _____

Name Site Contact: (Dr.) (Ms.) (Mrs.) (Mr.)

First: _____ Last: _____

Department _____

Phone Number _____ Alternative Number _____

Fax Number _____ Email _____

IS MESSAGE LEFT ON ANSWERING MACHINE/VOICE MAIL ACCEPTABLE? ☐ YES ☐ NO
IF "NO", PLEASE SPECIFY ALTERNATE METHODS:

1. _____ 3. _____

2. _____ 4. _____

ALTERNATIVE CONTACT

Site Name: _____

Name Site Contact: (Dr.) (Ms.) (Mrs.) (Mr.)

First: _____ Last: _____

Department _____

Phone Number _____ Alternative Number _____

Fax Number _____ Email _____

IS MESSAGE LEFT ON ANSWERING MACHINE/VOICE MAIL ACCEPTABLE? ☐ YES ☐ NO
IF "NO", PLEASE SPECIFY ALTERNATE METHODS:

1. _____ 3. _____

2. _____ 4. _____

NOTE: ***Please inform the core lab of any updates or changes in notification criteria and/or contact information. Failure to do so may result in a delay in notification.***

Name and signature of person completing this form

Print Name _____

Signature _____

Date _____

Please scan and email this form to:

Lisa M. Desiderio RT (R) (MR) CCRC
University of Pennsylvania Health System
Project Manager/ Neuroradiology Division
Phone: (215) 662-6573
Lisa.Desiderio@uphs.upenn.edu

Please copy the trial manager at the DCC:

Kinjal Shah, PA-C
Clinical Trial Manager
Tel: 212-659-8399
Cell Phone: 646-629-9649
Fax: 646-537-9312

Kinjal.Shah@mountsinai.org

APPENDIX N: MRI Incidental Findings Form

NEUROPROTECTION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT

INCIDENTAL FINDINGS FORM

Neuroradiologist Form

Participant ID: _____ **Scan Date:** _____

Findings that Require Routine Reporting to the PI (check one or more)

_____**Level 1 – Normal Brain MRI**

_____**Level 2 – Non-urgent referral. Any lesion(s) not usual for this cohort age and may present as a diagnostic lesion.(Check one or more):**
_____ non-specific white matter disease
_____ mild-moderate cerebral atrophy
_____ other non-urgent findings _____

_____ **Level 3 – Urgent disease related findings. (Check one or more):**
_____ sub-acute infarct
_____ arterial venous malformation
_____ obstructive hydrocephalus
_____ tumor without mass effect
_____ other urgent findings _____

Level 4 Findings Require Timely Notification of PI

_____**Level 4 – Immediate findings (Check one or more):**
_____Acute or subacute infarct
_____Acute or chronic subdural hematoma
_____Epidural hematoma
_____Subarachnoid hemorrhage
_____Aneurysm
_____Cerebral Tumor with abscess
_____Cerebral Abscess
_____Other immediate findings _____

PI Name: _____

Category 3 or 4 referral process: The field center radiologist will notify the proper site personnel as defined by the site principal investigator:

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NEUROPROTECTION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT

INCIDENTAL FINDINGS FORM

Telephone: Fax:

_____, **MD, Radiologist** Signature

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