Cardiothoracic Surgical Trials Network

Protocol

NEUROPROTECTION IN PATIENTS UNDERGOING AORTIC VALVE REPLACEMENT



Sponsored By NHLBI, NINDS, & CIHR
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TABLE OF CHANGES

Revision	Section	Change	Reason	Page
1.0	Cover Page	Changed date to September 2014	Protocol update	1
1.0	Abstract: 2^0 endpoints	Changed "filter" to "embolic protection device"	For internal consistency within protocol	10
1.0	Secondary Endpoints	Changed "filter" to "embolic protection device"	For internal consistency within protocol	16-17
1.0	Adverse Events	Added "for general reporting procedures and guidance on the determination of intervention-expected adverse events."	For clarity	22
1.0	Monitoring	Changed description of on-site monitoring visit schedule to approximately once each year depending on site enrollment	For consistency with DCC procedures	33
2.0	Cover Page	Changed date to February 2015	Protocol update	1
2.0	Definitions, Acronyms & Abbreviations	Updated list of acronyms	For internal consistency within protocol	6
2.0	Throughout document	Administrative changes	For internal consistency	Through out
2.0	Throughout document	Changed "treatment arm", "Embol-X" and other references to an FDA approved device to "legally marketed embolic protection devices"	To be inclusive of all applicable governing regulatory agencies	Through out
2.0	Abstract	Added CardioGard Emboli Protection Cannula to the list of treatment arms	Protocol update	9
2.0	Various sections	Added 3D-CAM at baseline	Protocol update	9, 17, 22, 29
2.0	Various sections	Changed sample size to up to 535 patients	Protocol update	10, 18
2.0	Various sections	Changed recruitment period to 24 months	Protocol update	10, 18
2.0	Data Collection Schedule	Added 3D-CAM at baseline	Protocol update	11
2.0	Embolic Protection	Added description of the CardioGard Cannula	Protocol update	15
2.0	Rationale for Selection of Endpoints	Added an allowance for 3.0T DWI-MRI to be used	Protocol update	16, 21, 32
2.0	Randomization, Treatment Interventions	Updated to include the CardioGard Cannula	Protocol update	18, 19-20
2.0	Qualifications and Training	Updated to include the CardioGard Cannula	Protocol update	27
2.0	Medications, Physical Exam	Changed window from -7 to -30 days	Protocol update	29
2.0	Medications	Added collection of analgesics and psychopharmacologics at Day 7	To assess their impact on delirium	31
2.0	Analytical Plan	Updated to include CardioGard cannula, exploratory analyses	Protocol update	34-37
2.0	Organization of the Study	Added the MRI and Histopathology Core Lab names	Protocol update	38
3.0	Throughout	Updated Rev to 3.0, October 2015 and included administrative changes including spelling and grammar updates	Protocol update	All
3.0	Inclusion Criteria	Updated age criterion to include patients age 60 and above	Protocol update	9, 20

3.0	Exclusion Criteria	Added current permanent pacemaker at baseline as a contraindication to MRI	Protocol update to ensure primary endpoint capture	9, 20
3.0	Exclusion Criteria	Added additional allowed concomitant procedures of LAA management, ASD closure and PFO closure	Protocol update	9, 20
3.0	Exclusion Criteria	Clarified timing of exclusion criterion of cardiogenic shock or treatment with IV inotropic therapy	Protocol update	9, 20
3.0	Secondary Endpoints	Clarified that either 1.5T or 3.0T is acceptable	Protocol update	10, 17, 21, 22, 32
3.0	Data Collection Schedule	Corrected schedule to indicate that physical examination is also required on Post-op Days 7 and 90	Protocol correction	12
3.0	Randomization	Added “after sternotomy and confirmation by the surgical team of the patient’s eligibility to receive any of the three treatment arms” for clarification	Protocol clarification	19, 31
3.0	Neurocognitive Testing	Changed baseline neurocognitive testing window from 7 days to 30 days pre-randomization	Protocol update	30
3.0	Medications	Clarified baseline medication collection	Protocol Clarification	30
3.0	Analytical Plan	Added information on a planned interim analysis	Protocol update	38-39

DEFINITIONS, ACRONYMS & ABBREVIATIONS

ABB	Approximate Bayesian bootstrap
ACGME	Accreditation Council for Graduate Medical Education
AE	Adverse event
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ALT	Alanine aminotransferase
AS	Aortic stenosis
ASD	Atrial septal defect
AST	Aspartate aminotransferase
AVR	Aortic valve replacement
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAM	Confusion Assessment Method
CFR	Code of Federal Regulations
CIHR	Canadian Institutes of Health Research
CNS	Central Nervous System
CPB	Cardiopulmonary bypass
Cr	Creatinine
CRF	Case report form
CT	Computed Tomography
CTA	Clinical Trial Agreement
CTSN	Cardiothoracic Surgical Trials Network
CV	Curriculum vitae
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
DUNCL	Duke University Neurocognitive Core Lab
DVT	Deep vein thrombosis
DWI	Diffusion-weighted imaging
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
EM	Electron microscopy
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
InCHOIR	International Center for Health Outcomes & Innovation Research
INR	International normalized ratio
IRB	Institutional Review Board
IQR	Inter-quartile range
LAA	Left atrial appendage

LBBB	Left bundle branch block
LDH	Lactate dehydrogenase
LOS	Length of stay
MCG	Medical College of Georgia
MI	Myocardial infarction
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
MVR	Mitral valve repair
NHLBI	National Heart Lung & Blood Institute
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
NYHA	New York Heart Association
OHRP	Office for Human Research Protections
PDC	Protocol Development Committee
PE	Pulmonary embolism
PFO	Patent foramen ovale
PI	Principal investigator
PT	Prothrombin time
PTT	Partial thromboplastin time
QoL	Quality of life
RCC	Ratio-of-Cost-to-Charges
REB	Research Ethics Board
SAE	Serious adverse event
SD	Standard deviation
SSL	Secure Socket Layer
T	Tesla
TEE	Transesophogeal echo
TIA	Transient ischemic attack
URL	Upper reference limit
UP	Unanticipated problem
VPN	Virtual Private Network

ABSTRACT

Clinical Significance	• Periprocedural ischemic neurological injury is prevalent after cardiac surgery in general and aortic valve replacement (AVR) in particular. • Perioperative neurological events significantly increase mortality, morbidity, and the costs of care. • High rates of new neuroradiographic (magnetic resonance imaging [MRI]) lesions following AVR have been found in small studies (32% (Cook et al. 2007)), 47% (Knipp et al. 2005)). • A more recent prospective cohort study (Acker, Messe; n=196) showed clinical strokes in 17% (4% of which were moderate/severe) and infarct on MRI was seen in 61%. Number (0-34) and volume (16-56000 mm^3) of lesions have varied greatly per patient (Messe et al. 2014). • Embolic protection devices have been shown to be safe and to capture emboli; however, there is a need for more rigorous data on their efficacy, including documentation of cerebral infarcts by both clinical assessments and radiographic studies.
Objectives	The overall objective of this study is to evaluate the efficacy and safety of embolic protection devices to reduce ischemic brain injury in patients undergoing surgical aortic valve replacement. • The primary aim of this trial is to evaluate the extent to which legally marketed embolic protection devices provide neuroprotection, defined as freedom from acute clinical or radiographic cerebral infarction within 7 (± 3) days post procedure, in patients undergoing aortic valve surgery. • The secondary aim of this trial is to assess the relationship of radiographic cerebral infarcts to clinical stroke endpoints and neurocognitive outcomes.
Study Design	This trial is a multicenter parallel-group randomized trial in which AVR patients will be randomized to legally marketed embolic protection devices versus standard care.
Target Population	Patients diagnosed with calcific aortic stenosis (AS) with planned AVR
Selected Eligibility Criteria	***Inclusion Criteria*** 1. Age ≥ 60 years 2. Planned and scheduled surgical aortic valve replacement via a full or minimal-access sternotomy (using central aortic perfusion cannulae) for calcific aortic stenosis with a legally marketed valve 3. No evidence of neurological impairment as defined by a NIHSS ≤1 and modified Rankin scale (mRS) ≤ 2 within 7 days prior to randomization 4. Ability to provide informed consent and comply with the protocol ***Exclusion Criteria*** 1. Contraindication to legally marketed embolic protection devices (e.g. aneurysm of the ascending aorta, aortic trauma, porcelain aorta, known sensitivity to heparin) 2. History of clinical stroke within 3 months prior to randomization 3. Cardiac catheterization within 3 days of the planned aortic valve replacement 4. Cerebral and or aortic arch arteriography or interventions within 3 days of the planned aortic valve replacement

	5. Active endocarditis at time of randomization 6. Anticipated inability to tolerate or contraindication for MRI (e.g., known intolerance of MRI, permanent pacemaker at baseline or expected implantation of a permanent pacemaker) 7. Any other concomitant aortic procedure such as root replacement 8. Concomitant surgical procedures other than CABG, mitral annuloplasty, left atrial appendage (LAA) management, atrial septal defect (ASD) closure or patent foramen ovale (PFO) closure 9. Clinical signs of cardiogenic shock or treatment with IV inotropic therapy prior to randomization 10. Concurrent participation in an interventional (drug or device) trial
Rx arms	Patients will be enrolled in equal allocation to one of the following: a) EMBOL-X® embolic protection device; b) CardioGard Emboli Protection Cannula; and c) Standard aortic cannula
1^0 Endpoint	The *primary efficacy endpoint* is freedom from clinical or radiographic CNS infarction at 7 (± 3) days post procedure.
2^0 Endpoints	*Composite Clinical Endpoint* o A composite endpoint of mortality, clinical stroke, and acute kidney injury within 30 days of surgery *Safety* o Serious adverse events within 90 days of surgery o Clinical stroke > 7 days post-surgery o Presence/absence of aortic lesions after decannulation *Emboli Captured* o Volume of emboli captured and volume of largest particle captured o Histological characteristics *Clinical and Radiographic Brain Injury* o Number of patients with clinical stroke within 7 (± 3) days post procedure o Volume of acute ischemic brain lesions assessed by 1.5 T (3.0 T is acceptable if 1.5 T not available) DWI at 7 (± 3) days post procedure o Number of acute ischemic brain lesions assessed by 1.5 T (3.0 T is acceptable if 1.5 T not available) DWI at 7 (± 3) days post procedure *Functional Status and Neurocognition* o Neurocognitive function in 6 domains (memory, information processing speed, executive function, language, attention, and visuospatial/constructional) assessed pre-operatively and at 90 (± 7) days post procedure o Neurological outcomes assessed by NIHSS pre-operatively and at 1, 3, 7 (± 3), 30 (± 7), and 90 (± 7) days; and assessed by the mRS and Barthel Index pre-operatively and at 30 (± 7) and 90 (± 7) days post procedure o Delirium assessed by the Confusion Assessment Method (CAM) scale pre-operatively and at 1, 3, and 7 (± 3) days post procedure *Survival* o All-cause mortality within 90 days of surgery *Hospitalization (≤ 90 days)*

	○ LOS of index hospitalization (including ICU days) ○ Number and reasons for readmissions ○ Days alive out of the hospital *Quality of Life* ○ SF-12 ○ Geriatric Depression Scale (GDS) *Economic* ○ Hospital resource utilization ≤ 90 days *Device Performance (treatment arm)* ○ Successful aortic access, delivery and retrieval of the embolic protection device ○ No need for additional surgery or re-intervention related to use of the embolic protection device ○ Intended function of the filter: ○ No migration, fracture or embolization ○ Capture of embolic material on gross inspection
Sample size	Up to 535 patients
Data and Safety Monitoring	An independent Data and Safety Monitoring Board (DSMB) will oversee patient safety and overall progress of the study. An independent Event Adjudication Committee (EAC) will review and adjudicate adverse events occurring during this trial. Stopping guidelines for safety will be developed based upon trial data.
Duration	Accrual is expected to take 24 months, and all patients will be followed for 90 (± 7) days following surgery

DATA COLLECTION SCHEDULE

Assessment	Screening/ Baseline	Intra-Op	Day 1 Post-Op	Day 3 Post-Op	Day 7 (± 3) Post-Op	Day 30 (± 7) Post-Op	Day 90 (± 7) Post-Op	Event Driven
General								
Informed Consent	X							
Release of Medical Information	X							
Screening Log and Registration	X							
Medical History	X							
Laboratory Assessment	X							X
Medications	X				X	X	X	X
Physical Exam	X				X		X	
Preoperative Cardiac Catheterization	X							
Eligibility Criteria	X							
Surgical Procedure		X						
Epiaortic Scan		X[1]						
DWI MRI					X			
Geriatric Depression Scale	X						X	
SF-12	X						X	
Neurocognitive Testing								
Hopkins Verbal Learning Test	X						X	
Trailmaking Tests A and B	X						X	
MCG Complex Figures	X						X	
Digit Span	X						X	
Digit Substitution Test	X						X	
COWA Verbal Fluency Test	X						X	
Neurological Assessments								
NIH Stroke Scale	X		X	X	X	X	X	X
Modified Rankin Scale	X					X	X	X
Barthel Index	X					X	X	
CAM Delirium Assessment	X		X	X	X			
Event Driven Data								
Adverse Events								X
Hospitalization	X							X

[1] Epi-aortic scan will be performed twice during surgery, once before placement of the cannula to assess degree of atherosclerosis and again after removal of the cannula to determine the presence or absence of aortic lesions

Missed Visit								X
Mortality								X
Study Completion/Early Termination							X	X
End of Study/Investigator Statement								X

OBJECTIVES

The overall objective of this study is to evaluate the efficacy and safety of embolic protection devices, approved for general use by the governing regulatory agencies, to reduce ischemic brain injury in the setting of surgical aortic valve replacement.

- The primary aim of this trial is to evaluate the extent to which the embolic protection devices provide neuroprotection, defined as freedom from acute clinical or radiographic cerebral infarction within 7 (± 3) days post procedure, in patients undergoing aortic valve surgery for aortic stenosis.
- The secondary aim of this trial is to assess the relationship of radiographic cerebral infarcts to clinical stroke endpoints and neurocognitive outcomes.

BACKGROUND AND SIGNIFICANCE

Periprocedural Neurological Adverse Events

Periprocedural adverse neurological events including ischemic cerebral injury remain prevalent after cardiac surgery in general. Periprocedural strokes are estimated to occur in 1.6-6.1% of patients undergoing cardiac surgery (Roach, Kanchuger et al. 1996; Ahlgren and Aren 1998; Salazar, Wityk et al. 2001; Hogue, Gottesman et al. 2008) ; stroke frequency in high-risk patients has been reported as high as 16% (Grogan, Stearns et al. 2008). The incidence of postoperative cognitive and neuropsychological dysfunction is estimated to exceed 50-80% at discharge (Bucerius, Gummert et al. 2003; Stolz, Gerriets et al. 2004) with risk of stroke in patients with advanced age is as high as triple the risk observed in younger patients (Craver, Puskas et al. 1999; Ngaage, Cowen et al. 2008).

Ischemic injury to the neurologic, renal, and cardiovascular systems after cardiovascular procedures may lead to death or permanent disability; decreased quality of life; and increased length of hospitalization, chance of admission to a secondary care facility upon hospital discharge, and health care costs (Roach, Kanchuger et al. 1996; Newman, Kirchner et al. 2001; Hogue, Palin et al. 2006; McKhann, Grega et al. 2006; Hogue, Gottesman et al. 2008). Greater than 40% incidence in cognitive decline at 5 years after CABG has been reported (Newman, Kirchner et al. 2001).

Stroke after cardiac surgery doubles the duration and cost of hospitalization, portends a 5-10-fold increase in early mortality, and imposes chronic disability on 69% of survivors (Puskas, Winston et al. 2000; Salazar, Wityk et al. 2001). As the population ages, the mortality, morbidity, and costs of care associated with perioperative neurological events will increase significantly. As of 2001, the economic impact of stroke after coronary revascularization was estimated to exceed $2-4 billion worldwide.

Among cardiac procedures, patients undergoing aortic valve replacement (AVR) are especially susceptible to peri-procedural neurological injury (Ahlgren and Aren 1998; Hogue, Murphy et al. 1999; Salazar, Wityk et al. 2001; Bucerius, Gummert et al. 2003). A literature search yielded 5 published studies that have performed early post-operative MRI in patients undergoing valve surgery. These studies all contain <50 patients, and many do not provide extensive information about the distribution of the DWI lesion data.

In brief, Stolz (2004) reviewed 37 patients, age 66± 10. Postoperative DWI lesions were present in 14 patients (38%). DWI lesion volume ranged from 0.1 to 24.8 cm^3 (median, 0.5 cm^3; mean, 3.8 (8.4 cm^3). (Stolz, Gerriets et al. 2004) Cook (2007) presented data on MRI from 50 patients who underwent cardiac surgeries, 22 aortic and/or mitral valve surgeries, age 73 ±5.(Cook, Huston et al. 2007) Postoperative

DWI lesions were present in 16 patients (32%). There were frequently multiple infarcts in patients but they tended to be small. There were 63 ischemic lesions in 16 patients. The group mean was 4 ± 5 infarcts per patient; three of 16 patients had greater than five infarcts. Of the 63 defects, only three were greater than 10 mm in diameter. The total ischemic volume was less than 1,000 mm^3 in 11 of 16 patients. Cognitive evaluations were performed on all patients, and cognitive decline was not associated with MRI infarcts in this study. Knipp (2005) presented 35 patients undergoing valve replacement with a mean age of 64.9 ± 9.8 years (Knipp, Matatko et al. 2005). Postoperative MRI detected new focal infarcts lesions in 14 patients (47%), although no clinical strokes were detected. Six patients (43%) had multiple (S3) lesions (range, 1–7). Lesion volume ranged from 50–500 mm^3 except one infarct of 1900 mm^3. Floyd (2006) presented results from 34 cardiac surgery patients with post-procedure MRI.(Floyd, Shah et al. 2006) Overall, there were 6 of 34 with new DWI lesions. However, the new radiographic infarcts occurred in the 15 AVR patients (40%). Among these individuals, the number of new lesions averaged 3 ± 3. The infarct size averaged less than 10 mm and the maximum diameter was 35 mm. Finally, Barber (2008) presented 37 patients with cardiac surgery and post-procedure MRI.(Barber, Hach et al. 2008) Sixteen of 37 participants (43%) had new ischemic lesions (range, 1-17 lesions). The distribution of the infarct data was not explicitly stated but the study did demonstrate a significant association between cognitive decline and postoperative ischemic lesions, as well as an association between the number of abnormal cognitive tests and ischemic burden.

The DeNOVO study (Messe SR 2013) is a prospective cohort of 196 patients over 65 years of age undergoing aortic valve replacement for calcific aortic stenosis with pre- and post-procedure neurologic evaluations, MRIs, and cognitive assessments. Post-procedure MRI was performed on 129 subjects. DWI lesions were seen in 79 patients (61%), and the number of lesions per patient ranged from 0 – 34. The mean number of lesions per patient was 2.3 (SD 4.6) and the median was 1 (IQR 0-3). No DWI lesions were seen in 51 patients (40%), 43 (33%) had 1 or 2 lesions, and 34 (27%) had 3 or more lesions. The total volume of DWI lesions per patient ranged from 16 – 55871 mm^3.

Embolic Protection Devices

Multiple studies over the past 20 years have shown a relationship among aortic atherosclerosis, particulate debris released during cardiac surgery, and injury to distal organs (Mills 1995; Roach, Kanchuger et al. 1996; Stump, Rogers et al. 1996; Wolman, Nussmeier et al. 1999; Vaage, Jensen et al. 2000; Borger, Ivanov et al. 2001; Murkin 2001). Cardiac surgeons first used intraaortic filtration to capture and remove particulate emboli during surgery to reduce the risk of perioperative complications related to atheroemboli in 1999 (Schmitz, Weinreich et al. 2003). Though MRI and autopsy studies have confirmed emboli in the kidneys, gastrointestinal tract, and lower extremities (Blauth, Cosgrove et al. 1992) as well as in the brain (Moody, Brown et al. 1995) after cardiac surgery, most studies of intraaortic filtration have focused on either the ability of the device to successfully capture particulate emboli (Harringer 2000; Reichenspurner, Navia et al. 2000; Bergman, Hadjinikolaou et al. 2002; Christenson, Vala et al. 2005; Horvath and Berry 2005; Sobieski, Pappas et al. 2005; Mestres, Bernabeu et al. 2007) or neuroprotection (Schmitz and Blackstone 2001; Eifert, Reichenspurner et al. 2003; Schmitz, Weinreich et al. 2003; Wimmer-Greinecker 2003) using the Edwards EMBOL-X® intraaortic filter. Results indicate that intraaortic filtration can successfully remove debris. Particulate matter was captured in 94.5-100% of deployed filters in the studies referenced above. The number of particles captured per filter ranged from 0 – 74 with particle surface area ranging from 0.1 – 188 mm^2. Captured embolic particles were most often

composed of fibrous atheroma (54-79%). Fibrin, true thrombus, medial tissue, normal vessel wall, mature hyaline cartilage, fat, and suture material were also found.

Several larger studies were designed to compare neurologic outcomes in patients undergoing cardiac surgery with the use of intra-aortic filtration to expected rates of neurologic events based on the Multicenter Study of Perioperative Ischemia (McSPI) Risk Index (Schmitz and Blackstone 2001; Wimmer-Greinecker 2003). Higher risk patients who received intraaortic filtration were less likely to experience neurological events than expected. A randomized, controlled trial evaluating neurologic events (stroke, TIA, coma, delirium, and memory deficit) found a trend towards fewer neurologic events (Schmitz, Weinreich et al. 2003). Again, higher risk patients appeared to receive more benefit though the trend did not reach statistical significance.

The largest randomized study to date of an early version of the EMBOL-X® device, the ICEM 2000 trial, examined a composite endpoint of mortality, stroke, TIA, renal injury, myocardial infarction, gastrointestinal complications, and limb-threatening ischemia and evaluated these endpoints individually (Banbury, Kouchoukos et al. 2003). In addition, histologic evidence was collected from the filters. Patients who were at least 60 years of age and undergoing an isolated cardiac procedure (CABG, aortic valve replacement, or mitral valve repair or replacement) using cardiopulmonary bypass were enrolled. Reoperations, combined cardiac procedures (e.g. combined CABG and valve surgery), and repairs/replacements of the ascending aorta were excluded, as were patients with fixed neurologic defects, renal failure, ascending aortic aneurysms, or hemodynamic instability. Emboli were captured in 96.8% of the filters deployed in this study. There was no difference in clinical endpoints between the filtered and unfiltered arms, but a post-hoc analysis of higher risk patients showed a significant reduction in the composite clinical endpoint and in renal complications alone in the filtered arm compared to the unfiltered arm. The ICEM 2000 trial involved predominantly CABG patients, and no DWI MRI imaging or neurocognitive testing was performed.

The CardioGard embolic protection cannula employs a different strategy to capture emboli during cardiac surgery. Instead of intra-aortic filtration, it extracts emboli through a suction tube located posteriorly to the main forward-flow tube of an aortic perfusion cannula. A multi-center randomized clinical trial was recently conducted to examine the safety and efficacy of the device (Bolotin, Huber et al. 2014). This trial of 66 adult patients undergoing elective AVR with or without CABG showed a significant reduction in the total volume of new brain lesions measured by DW-MRI at 5-7 days post-surgery and a significant reduction in the number of patients with any new brain lesions at 5-7 days post-surgery compared to a standard aortic cannula. The volume of new brain lesions for the treatment group was (mean±SE of mean) 44.00±64.00 vs 126.56±28.74 mm^3 in the control group. In the treatment group, 41% demonstrated new postoperative lesions compare to 66% in the control group. The complication rate was comparable in both groups. Whereas this trial offers promising clinical results based on DWI MRI imaging, the sample size was small and neurocognitive endpoints were not included. Further clinical trials that focus on an elderly AVR population, who are at high risk of neurological adverse events, and that utilize rigorous methods to image brain injury and assess neurocognition, are needed.

Rationale for Selection of Endpoints

Diffusion-weighted magnetic resonance imaging (DWI) has been proposed as a surrogate marker for brain embolism and brain injury. Rates of new brain lesions detected using diffusion weighted imaging (DWI) following AVR have been reported in a range of studies described above. The largest of these is a prospective cohort study (Messe SR 2013), which showed clinical strokes in 17% and neuroradiographic lesions in 61%. The results from the DeNOVO study (Messe SR 2013) are substantially similar to the smaller published studies of MRI findings after AVR. Importantly, the MRI outcomes in DeNOVO are also similar to the results from the ENACT study (Hill, Martin et al. 2012), the neuroprotectant study in patients undergoing aneurysm coiling. Taken together, these data suggest that there are a number of MRI measures that could be used for a neuroprotectant trial in patients undergoing AVR. Because some studies have shown that accuracy in stroke diagnosis has shown to be superior with 1.5-T DWI compared to 3.0-T DWI (Rosso, Drier et al. 2010) and is believed to better accommodate patients with pacemakers, 1.5-T DWI will be required to be used for endpoint assessment in those sites that have such a scanner. For those sites that have only a 3.0 T machine, this scanner can be used and the core lab will analyze with a 3-T specific algorithm. Sites will not be allowed to switch between different types of scanners.

ENDPOINTS

Primary

The *primary efficacy endpoint* is freedom from acute CNS infarction at 7 (± 3) days post procedure.

Secondary

Secondary endpoints include assessments of brain lesions, neurological outcomes, and adverse events, specifically:

Composite Clinical Endpoint

- A composite endpoint of mortality, clinical stroke, and acute kidney injury within 30 days post-surgery

Safety

- Serious adverse events within 90 days post-surgery
- Clinical stroke > 7 days post-surgery
- Presence/absence of aortic lesions after decannulation

Emboli Captured

- Volume of emboli captured and volume of largest particle captured
- Histological characteristics

Radiographic Brain Lesions

- Volume of acute ischemic brain lesions assessed by 1.5 or 3.0 T DWI at 7 (± 3) days post-surgery
- Number of acute ischemic brain lesions assessed by 1.5 or 3.0 T DWI-at 7 (± 3) days post-surgery

Functional Status and Neurocognition

- Neurocognitive function in 6 domains (memory, information processing speed, executive function, language, attention, and visuospatial/constructional) assessed pre-operatively and at 90 (± 7) days post procedure

- Neurological outcomes assessed by NIH Stroke Scale (NIHSS) pre-operatively and at 1, 3, 7 (± 3), 30 (± 7), and 90 (± 7) days post procedure; and assessed by the modified Rankin Scale (mRS) and Barthel Index pre-operatively and at 30 (± 7) and 90 (± 7) days post procedure
- The 3D-CAM (or CAM ICU, as appropriate) delirium scale will be administered pre-operatively and at 1, 3, and 7 (± 3) days post procedure

Survival

- All-cause mortality

Hospitalization

- LOS of index hospitalization (including ICU days)
- Readmissions

Quality of Life

- Quality of life will be measured with the SF-12 pre-operatively and at 90 (± 7) days post procedure
- Symptoms of depression will be assessed using the Geriatric Depression Scale (GDS) pre-operatively and at 90 (± 7) days post procedure

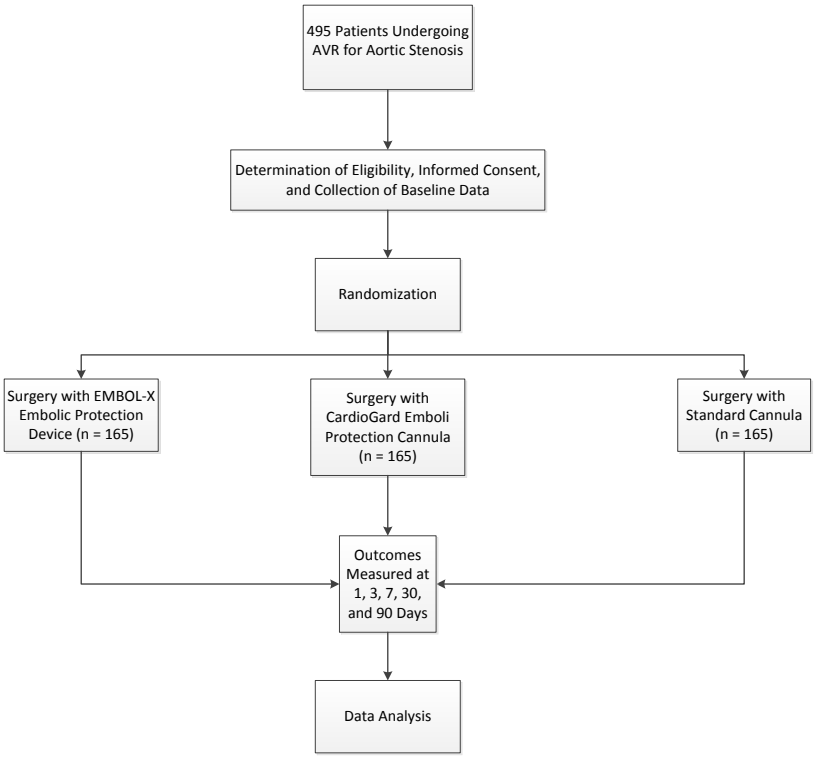
Economic

- Hospital resource utilization

Device Performance (treatment arm)

- Successful aortic access, delivery and retrieval of the embolic protection device
- No need for additional surgery or re-intervention related to use of the embolic protection device
- Intended function of the filter:
  - No migration, fracture or embolization
  - Capture of embolic material on gross inspection

Figure 1: Study Flowchart



STUDY DESIGN

This study is a prospective, multicenter, parallel-group randomized controlled clinical trial that will compare each embolic protection device (Edwards EMBOL-X® embolic protection device and the CardioGard embolic protection cannula) to a standard cannula. The enrollment period is expected to last 24 months (N=up to 535), and all patients will be followed for 90 (± 7) days post procedure. Endpoints

will be measured at 1, 3, 7 (± 3), 30 (± 7), and 90 (± 7) days post procedure. (See **Figure 1** for Study Flowchart)

RANDOMIZATION

Patients will be randomly assigned to one of the two embolic protection devices or to a standard cannula in the OR immediately after sternotomy and confirmation by the surgical team of the patient's eligibility to receive any of the three treatment arms. Randomization will be with equal allocation into all arms and stratified by site and by procedure (i.e., isolated AVR versus combined procedures such as AVR + CABG, AVR + MVR, and AVR + MVR + CABG). The randomization assignment will be controlled centrally and performed through a web-based data collection system that automates the delivery of the randomization codes. From the point of treatment assignment, primary efficacy will be analyzed by intention-to-treat; that is, the patients will be grouped by their assignments at randomization regardless of whether or not they actually received the treatment to which they were assigned.

MASKING

The nature of the study precludes masking surgeons from treatment assignment. Investigators will, however, be blinded to all data from other clinical sites, except serious unexpected AEs for Institutional Review Board (IRB)/Research Ethics Board (REB) reporting purposes. Clinical events including serious and protocol-defined adverse events will be reviewed by an Event Adjudication Committee. All MRIs and neurocognitive scoring will be analyzed by core laboratory personnel who will be blinded to treatment assignment and clinical outcomes.

STUDY POPULATION

The patient population for this trial consists of elderly patients undergoing surgical aortic valve replacement via full or minimal-access sternotomy for aortic stenosis using a legally marketed valve. Specific inclusion and exclusion criteria are listed below. All patients who meet the eligibility criteria may be included in the study regardless of gender, race, or ethnicity.

Inclusion Criteria

1. Age $\geq$ 60 years
2. Planned and scheduled surgical aortic valve replacement via a full or minimal-access sternotomy (using central aortic perfusion cannulae) for calcific aortic stenosis with a legally marketed valve
3. No evidence of neurological impairment as defined by a NIHSS $\leq$1 and modified Rankin scale (mRS) $\leq$ 2 within 7 days prior to randomization
4. Ability to provide informed consent and comply with the protocol

Exclusion Criteria

1. Contraindication to legally marketed embolic protection devices (e.g. aneurysm of the ascending aorta, aortic trauma, porcelain aorta, known sensitivity to heparin)
2. History of clinical stroke within 3 months prior to randomization
3. Cardiac catheterization within 3 days of the planned aortic valve replacement
4. Cerebral and or aortic arch arteriography or interventions within 3 days of the planned aortic valve replacement
5. Active endocarditis at time of randomization
6. Anticipated inability to tolerate or contraindication for MRI (e.g., known intolerance of MRI, permanent pacemaker at baseline or expected implantation of a permanent pacemaker)
7. Any other concomitant aortic procedure such as root replacement

8. Concomitant surgical procedures other than CABG, mitral annuloplasty, LAA management, ASD closure or PFO closure
9. Clinical signs of cardiogenic shock or treatment with IV inotropic therapy prior to randomization
10. Concurrent participation in an interventional (drug or device) trial

Recruitment Strategies
Open AVR is a prevalent cardiac surgical procedure conducted within the participating Network centers. We will establish enrollment targets for each clinical site based on a review of pre-screening logs. Enrollment strategies may include 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. The DCC will regularly assess actual enrollment in relation to pre-specified goals, and additional interventions to facilitate enrollment will be implemented as needed. The Pre-Screening Failure Log will identify numbers of patients screened and reasons for ineligibility and/or non-enrollment into the trial.

Inclusion of Women and Minorities
The inclusion of women and minorities in clinical trials is critical for scientific, ethical, and social reasons and for the generalizability of trial results. The Network is strongly committed to ensuring a balanced recruitment of patients regardless of sex or ethnicity. The CTSN intends to recruit at least 30% women and 25% minorities in this trial. The following measures will be employed to ensure adequate representation of these groups:

- Documentation of the number of women and minorities screened and enrolled via screening and exclusion logs;
- Monitoring of such logs from each clinical center on a monthly basis;
- If necessary, the development and implementation of outreach programs designed to recruit adequate numbers of women or minorities.

TREATMENT INTERVENTIONS
All patients enrolled in this trial will undergo surgical aortic valve replacement for aortic stenosis. Patients will be randomly assigned to the following treatment groups:

- *Embolic protection device (Edwards EMBOL-X®)*
- *Embolic protection device (CardioGard Emboli Protection Cannula)*
- *Standard aortic cannula*

Surgical procedures are performed by either a full or limited access sternotomy. In patients assigned to the standard cannula group, standard cannulation techniques are performed using any standard aortic cannula of the surgeon's choice. In those patients assigned to either embolic protection device group, the Edwards EMBOL-X® device or the CardioGard Emboli Protection Cannula is used instead, per the manufacturer's instructions for use (IFU).

For patients assigned to the Edwards EMBOL-X® device, the surgeon may use either the EMBOL-X® Access Device/Aortic Cannula or a standard cannula with the EMBOL-X® filter deployed through a separate introducer sheath. The EMBOL-X® filter consists of a heparin-coated polyester mesh with pore size designed to capture particulate emboli with diameters of more than 120 µm. The flexible wire filter frame allows the filter to conform to the interior diameter of ascending aorta. The size of the distal ascending aorta is determined either by CT scan or intraoperative direct aortic measurement (TEE or epi-aortic ultrasound). The filter size is then selected based on the measured aortic size. The available filter sizes range from 26 mm to 37 mm. The filter is prepared and kept in saline until it is ready to load the

filter into the filter introducer sheath to minimize potential air bubbles in the filter. The filter is deployed in the ascending aorta before the aortic cross clamp is placed and subsequently removed. A new filter should be deployed prior to removal of the aortic cross clamp and remains in place until the patient is weaned from cardiopulmonary bypass. It is recommended that the filter be exchanged after 60 minutes of deployment to avoid platelet aggregation on the filter. The standardization of the surgical technique is described in the operations manual.

The CardioGard embolic protection device is a curved tip 24-French aortic perfusion cannula, comprised of 2 hollow tubes. The first tube is the standard main forward-flow tube. The second tube attached to an existing bypass vent port, is a novel element located posteriorly to the main tube; its function is to facilitate blood and particle suction by directing the blood back to the reservoir of the coronary bypass machine, while the retrieved embolic material is eliminated through the filter of the venous reservoir. The surgeon will use standard cannulation techniques to insert the aortic perfusion cannula.

DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoint

The primary efficacy endpoint is the freedom from CNS infarction within 7 days, defined as brain, spinal cord, or retinal cell death attributable to ischemia based on neuropathological, neuroimaging, or clinical evidence of permanent injury based on symptoms persisting $\geq$ 24 hours, with overt symptoms or no known symptoms (Sacco, Kasner et al. 2013). All patients will be assessed by 1.5 or 3.0 T DWI at 7 ($\pm$ 3) days post procedure for presence of brain lesions and to measure the number and volume of any present lesions. The proportion of patients with CNS infarction will be compared between groups.

Secondary Endpoints

Secondary endpoints for the trial are defined as follows:

Composite Clinical Endpoint

The proportion of patients who have had a clinical ischemic stroke, acute kidney injury (AKI), or death within 30 days of surgery will be compared by group. Clinical stroke and AKI are defined below.

Clinical Stroke

A new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note) that lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction on neuroimaging). This definition focuses on ischemic stroke, including hemorrhagic conversion of an ischemic stroke. The NIH Stroke Scale (NIHSS) must be administered within 24 hours following the event if the event is not captured at a protocol-defined assessment time point to document the presence and severity of neurological deficits.

Acute Kidney Injury (AKI)

AKI is defined according to the Acute Kidney Injury Network (AKIN) criteria (Mehta, Kellum et al. 2007): An abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl ($\geq$ 26.4 μmol/l), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours). AKI is further classified according to Table 1 below.

Table 1: AKI Staging Criteria

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2[b]	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3[c]	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dl [≥ 354 μmol/l] with an acute increase of at least 0.5 mg/dl [44 μmol/l])	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours

Safety
Any serious or protocol defined adverse events within 90 days after surgery will also be analyzed. We will use epi-aortic scanning before and after cannulation to assess atheroma burden in the aorta to provide supporting evidence for events that may occur. Additional data will be collected on surgeries that are delayed or cancelled for an adverse reaction due to study device and compared by treatment group.

Emboli Captured
EMBOL-X® and CardioGard filters will be processed by a histology core laboratory using electron microscopy (EM). The total volume of emboli captured by the filters will be determined by the core laboratory. The volume of the single largest particle captured by each filter will also be reported. As emboli will only be captured in the active treatment arm, there will be no comparison between groups.

Clinical and Radiographic Brain Injury
The volume and number of brain lesions will be measured using 1.5 or 3.0 T DWI at 7 days post procedure. The proportion of patients who experience a non-silent stroke within 90 days post procedure will be compared between groups, and the time to first stroke will be compared between the two groups.

Neurological
Neurocognition will be compared between groups. Cognitive performance will be assessed across six different domains using the following battery of tests: Hopkins Verbal Learning Test (memory); Trailmaking Tests A and B (executive function); MCG Complex Figures (visuospatial/ constructional); Digit Span (attention); Digit Symbol Substitution Test (information processing speed); and COWA Verbal Fluency Test (language). Neurocognitive testing will be administered by clinical site personnel, who have been trained and certified for test administration by the Neurocognitive Core lab personnel. All neurocognitive test scoring will be performed centrally by the CTSN Neurocognition Core Lab. Neurocognition endpoints will be assessed at pre-surgical baseline and 90 days post procedure.

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 and therefore cannot perform the batteries, the completion of the batteries will not be required and will not preclude them from participating in the trial.

[b] 200% to 300% increase = 2- to 3-fold increase.
[c] Given wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT.

Neurological outcomes will be assessed by the NIHSS at 1, 3, 7 (± 3), 30 (± 7), and 90 (± 7) days post procedure and by the mRS and Barthel Index at 30 (± 7) and 90 (± 7) days post procedure. These assessments will be administered by neurology trainees or study coordinators who are certified to administer the assessments.

Incidence of delirium will be compared between groups. For patients who are extubated, the 3D-CAM assessment will be administered by neurology trainees or study coordinators who are trained and certified to administer the 3D-CAM; patients who remain intubated at the time of assessment will be evaluated using the CAM-ICU assessment. Delirium will be assessed pre-operatively and at days 1, 3, and 7 (± 3) days post procedure.

Survival
All-cause mortality will be assessed.

Hospitalizations

Length of Index Hospitalization
Overall length of stay for the index hospitalization will be measured and broken down by days spent in the ICU versus days spent on telemetry and regular floors. Discharge disposition will also be captured.

Readmissions
Readmission rates will be calculated for the first 30 days following intervention and for the duration of follow-up. Hospitalizations will be classified for all causes including for cardiovascular readmissions.

Quality of Life
Quality of life (QOL) will be measured at baseline and at 90 (± 7) days post procedure using the Short Form-12. The SF-12 is a general health status measure that examines 8 quality of life dimensions (physical activity, social activity, role/physical, body pain, general mental health, role/emotional, vitality and general health perception). For this trial, the SF-12 is available in English, Spanish and French. Inability to read and complete these instruments in the available languages does not preclude a patient from enrollment in the trial (a family member may assist in completing the QOL questionnaires). A copy of the SF-12v2 can be found in

Appendix V: SF-12v2.

Symptoms of depression will be assessed using the Geriatric Depression Scale (GDS). A score of 10 or below indicates absence of depression, while a score of 11 or higher is indicative of depression. Depression will be assessed pre-operatively and at 90 (± 7) days post procedure. A copy of the GDS can be found in Appendix VI: Geriatric Depression Scale.

Adverse Events

Please refer to the CTSN Clinical and Adverse Event Reporting and Adjudication Procedures guidance document for general reporting procedures and guidance on the determination of intervention-expected adverse events.

Specific Adverse Event Definitions

Aortic Dissection

A disruption of the intima of the aorta established by imaging (e.g., chest x-ray, chest CT or echocardiogram)

Bleeding

A bleeding event is defined by any one of the following:

- Transfusion of > 5 units RBC within the first 24 hours following surgery
- Death due to hemorrhage
- Re-operation for hemorrhage or tamponade

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias

Any documented arrhythmia that *results in clinical compromise* (e.g., hemodynamic compromise, oliguria, pre-syncope or syncope) that requires hospitalization or requires a physician visit or occurs during a hospital stay.

Cardiac arrhythmias are classified as follows:

- Cardiac arrest
- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
- Cardiac conduction abnormalities or sustained bradycardia requiring permanent pacemaker placement

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g., increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Pleural Effusion

Accumulation of fluid or clot in the pleural space documented by chest radiogram or chest CT that requires evacuation with surgical intervention or chest tube placement.

Pneumothorax

Presence of gas in the pleural space, documented by chest radiogram or chest CT, which requires evacuation or prolongs the duration of chest tube drainage.

Hepatic Dysfunction

Liver injury **and** impaired liver function defined as:

- ALT ≥ 3xURL *and* total bilirubin* ≥ 2xURL (>35% direct), **or**
- ALT ≥ 3xURL *and* INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xURL and total bilirubin ≥ 2xURL, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Major Infection

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). 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 general categories of infection are listed below:

Localized Infection

Infection localized to any organ system or region (e.g., mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Endocarditis

Signs, symptoms and laboratory findings consistent with endocarditis, including but not limited to fever ≥ 38.0° C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of new, intra-cardiac vegetation with or without other signs and symptoms should be considered adequate evidence to support the diagnosis of endocarditis. TEE should be the modality of choice for diagnosis of prosthetic valve endocarditis.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction[1]:

[1] Joint ESC/ACCF/AHA/WHF Task for the Redefinition of Myocardial Infarction, *Circulation*. 2007; 116:0-0.

Myocardial Infarction (Non-Procedure Related)

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Peri-CABG Myocardial Infarction

For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft of native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

Peri-Percutaneous Intervention (PCI) Myocardial Infarction

For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

Note: Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

Neurologic Dysfunction

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note) that is not classified as a clinical stroke. The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction on neuroimaging). The NIH Stroke Scale (NIHSS) must be administered within 24 hours following the event if the event is not captured at a protocol-defined assessment time point to document the presence and severity of neurological deficits.

Each neurological event must be subcategorized as:

- Transient Ischemic Attack (TIA), defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.
- Hemorrhagic stroke
- Ischemic stroke (after 30 days post procedure)
- Toxic Metabolic Encephalopathy, defined as a 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.

- Seizure, defined as an abnormal paroxysmal cerebral neuronal discharge that results in alteration of sensation, motor function, behavior, or consciousness
- Other

Renal Failure
New requirement for hemodialysis related to renal dysfunction. This definition excludes aquapheresis for volume removal alone.

Respiratory Failure
Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue ventilator support within 48 hours post-surgical intervention. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Heart Failure
Signs of inadequate organ perfusion or congestion, or a syndrome of compromised exertional tolerance manifested by dyspnea or fatigue that requires
- intravenous therapy (diuretics, inotropic support, or vasodilators) *and* prolongs hospital stay in the judgment of the investigator, ***or***
- introduction of intravenous therapy (diuretics, inotropic support, or vasodilators) at any point following discharge from the index hospitalization, ***or***
- readmission for heart failure

Arterial Non-CNS Thromboembolism
An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:
- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

Venous Thromboembolic Event
Evidence of venous thromboembolic event (e.g., deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence
Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical replacement.

Other
All other serious adverse events (events that cause clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay).

CLINICAL CENTERS
The study will be conducted in up to 25 clinical centers participating in the NIH-supported Cardiothoracic Surgery Network (CTSN). Each clinical center will be required to obtain IRB/REB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the Data

Coordinating Center with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile

The following information will be collected for all surgeons, neurologists, coordinators and other investigators who participate in the study: contact information including address, telephone, fax, beeper, and email. The surgeon, cardiologist, neurologist, and coordinator must provide their CVs, Conflict of Interest Statement and Financial Disclosure Certifications, and Institutional Health Insurance Portability and Accountability Act (HIPAA) Certificates to the DCC prior to initiation of enrollment.

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in surgical replacement of aortic valve and neurologists with experience in assessing strokes. To qualify as a surgeon participating in this trial, the surgical investigator must have performed at least 10 aortic valve replacement procedures annually (averaged over a 2 year period). The surgical investigator will receive onsite training from the device manufacturers and use the EMBOL-X® device in one or two procedures. Surgical investigators and perfusionists will receive training and use the CardioGard Emboli Protection Cannula in one or two procedures prior to enrolling patients in this randomized study. The certified surgeons will either perform the aortic procedure on their own enrolled patient, or participate in the aortic procedure of an enrolled patient whose surgeon is not certified. Surgical qualifications for all participating surgical investigators will be collected on the Surgical Certification Form and faxed to the DCC prior to accreditation. The clinical site Principal Investigator (PI) will be responsible for overseeing the ongoing performance of the other participating surgical investigators at that site over the course of the study. Participating neurologists must be currently either participating in an ACGME-accredited neurology residency, board certified or board eligible. Neurologists, neurology trainees and study coordinators must be trained and certified to administer the NIHSS, mRS and CAM.

Each clinical site will be certified for the acquisition of the 7 (± 3) day post-operative MRI by the MRI Core Lab, as defined in the Manual of Operations.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. The study coordinators will be trained by the CTSN Duke University Neurocognition Core Lab to administer the neurocognitive testing. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

Delegation of Authority and PI Oversight

Principal Investigators are responsible for all study activities at their sites. They may delegate study tasks to qualified staff members while continuing to oversee all study activities. The Delegation of Authority Log will list each staff member's title and responsibilities for the study. The PI is responsible for careful review of each staff member's qualifications. Each task should be assigned to more than one staff member to ensure proper coverage. Only staff members delegated for each task on the Delegation of Authority Log are to conduct study-specific assessments. The Delegation Log will also contain the signature of each staff member. The PI will initial any additions to the Delegation of Authority Log that occur during the course of the study. The PI should document oversight of study activities throughout the life of the trial by indicating review of key elements such as eligibility, abnormal laboratory values and adverse events via signature and date on appropriate source documentation.

Conflict of Interest and Financial Disclosure Agreement

This statement verifies that an investigator has no conflict of interest with any institution that may influence his/her participation in this study. All investigators need to complete this statement. Investigators will also submit a financial disclosure agreement.

Site Approval

The following documents must be collected prior to site approval:

- Fully executed Clinical Trial Agreement (CTA) with the CTSN DCC: InCHOIR, Department of Health Evidence and Policy, Icahn School of Medicine at Mount Sinai
- Curricula vitae
- IRB/REB roster
- IRB/REB approval, version and date for protocol and consent
- HIPAA compliance approval
- Dangerous Goods Certification Training
- Surgical and Neurological Investigator Certification
- MRI Lab Certification
- NIH Stroke Scale Training Certification
- Modified Rankin Scale Certification
- Neurocognitive Training Certification
- Site Delegation of Authority Log
- Clinical Center Laboratory Certification
- Laboratory normal ranges

Other regulatory and training documentation may be required prior to site initiation.
Prior to enrolling a patient, representatives from the DCC will conduct a site initiation for all investigators, coordinators, neurologists, radiologists, and any other health care professionals who may be involved in the study.

Patient Confidentiality

All patients' records will be kept confidential according to HIPAA guidelines. Study Investigators, site IRBs/REBs, the DCC, EAC, medical monitors, FDA, Health Canada and NHLBI personnel may review source documentation as necessary but all unique patient and hospital identifiers will be removed from source documents which are sent to the DCC. The aggregate data from this study may be published as per publication policy documented in the CTA; however, no data with patient identifiers will be published.

SCREENING AND BASELINE

Pre-Screening Failure Form

Prior to informed consent

Prior to approaching a patient to begin the informed consent process, the study personnel will review data on prospective patients to determine eligibility for inclusion in the trial.

All pre-screened patients (patients who are not consented) who are not enrolled are recorded in the Pre-screening Failure form. The data collected are HIPAA compliant and do not include patient identifiers but do include screening quarter, screening year, age, gender, and reason(s) not eligible or not enrolled.

Consent

Prior to screening data collection and protocol-defined procedures

Prior to screening, a thorough explanation of the risks and benefits of the study will be outlined by the PI 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, the consent process must begin at least the day before randomization and 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.

Release of Medical Information Form

Prior to screening data collection and protocol defined procedures

The patient must sign the Release of Medical Information form or institutional equivalent that authorizes release of medical records, including hospital costing data, to the study sponsors, investigators and monitors.

Demographics Form

At initiation of screening

A screened patient is defined as someone (a consented patient) who was referred to, or identified at a clinical site for consideration of entry into, the study and for whom some preliminary (i.e., medical record) data have been collected and/or reviewed. For all patients screened, date of birth, ethnic origin, and sex will be captured on the registration form. The EDC will generate a unique 5-digit identification code that will identify the patient throughout the course of the study.

Medical History

Within 7 days prior to randomization

This form captures the information pertaining to the medical history including but not limited to previous myocardial infarction, myocardial revascularization, stroke, and other comorbidities such as diabetes and peripheral vascular disease. Information regarding the current medical condition is also captured including but not limited to disposition at time of screening (outpatient, inpatient, ICU, etc).

Medications

Within 30 days prior to randomization

This form captures all categories of medications (including but not limited to cardiovascular, analgesic and psychopharmacological medications) at one pre-operative time point.

Physical Examination

Within 30 days prior to randomization

This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Preoperative Cardiac Catheterization

If performed within 30 days prior to randomization as standard of care

This form will capture the timing of the preoperative cardiac catheterization and whether the aortic valve was crossed with a catheter during the procedure.

Neurocognitive Testing

Within 30 days prior to randomization

Cognitive performance will be assessed at pre-surgical baseline using the following battery of tests, which are available in English, Spanish and French language versions: Hopkins Verbal Learning Test; Trailmaking Tests A and B; MCG Complex Figures; Digit Span; Digit Symbol Substitution Test; and COWA Verbal Fluency Test (Appendix I). Study personnel, trained and certified by the CTSN Neurocognitive Core Lab located at Duke University (DUNCL) in accordance with the respective neurocognitive tool, must conduct these tests and document the results on the appropriate forms. The

testing will take a total of 45 minutes and can be performed with a minimal amount of special equipment. Results from these tests will be independently scored at the DUNCL. All neurocognitive batteries will be digitally recorded and the de-identified recordings sent to the DUNCL for quality assurance evaluation.

CAM Assessment
Within 7 days prior to randomization
The 3D-CAM will be administered by a neurology trainee or study coordinator trained in the 3D-CAM.

Modified Rankin Scale
Within 7 days prior to randomization
The mRS will be administered by a neurology trainee or study coordinator trained in the mRS.

NIH Stroke Scale
Within 7 days prior to randomization
The NIHSS will be administered by a neurology trainee or study coordinator trained in the NIHSS.

Barthel Index
Within 7 days prior to randomization
The Barthel Index will be administered by a neurology trainee or study coordinator trained in the Barthel Index.

Quality of Life
Within 7 days prior to randomization
The SF-12v2 questionnaire will be completed by the patient to assess quality of life.

Depression
Within 7 days prior to randomization
The GDS will be administered by study staff trained to administer the GDS.

Laboratory Assessment
Within 30 days prior to randomization

- Hematology, including white blood cell *($10^3/\mu l$)*, Hemoglobin *(g/dl)*, Hematocrit *(%)*, Platelet count *($10^{3P}/\mu l$)*
- Coagulation profile, including prothrombin time (PT/sec), partial thromboplastin time (PTT/sec), International Normalized Ratio (INR)
- Blood chemistries, including sodium *(mM/L)*, potassium *(mM/L)*, blood urea nitrogen *(*BUN, *mg/dl)*, creatinine *(mg/dl)*
- Liver function tests, including total bilirubin *(mg/dl)*, alanine aminotransferase (ALT, *U/L)*, aspartate aminotransferase (AST, *U/L)*, albumin *(g/dl)*.

Eligibility Criteria/Eligibility Evaluation Form
Prior to randomization
The inclusion and exclusion criteria will be documented by the clinical site study coordinator and verified with the site PI in the Eligibility Evaluation Form. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Eligibility Evaluation Form. The data collected are HIPAA compliant and include reason for not being randomized. A representative from the DCC will be available to discuss any questions regarding patient eligibility.

RANDOMIZATION

The randomization procedure will be performed inside the OR immediately after sternotomy and confirmation by the surgical team of the patient's eligibility to randomize to any of the three treatment arms to minimize the chance of a randomized patient not participating in the trial. Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system once the checklist of inclusion and exclusion criteria has been completed and verified. For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated.

PROCEDURE

Surgical Procedure

Initial surgical intervention

The initial surgical procedure (open AVR) must be reported on the surgical procedure form within 48 hours of the event. Operative data such as cross-clamp time, additional procedures performed at the time of the operation, and intra-operative blood transfusions, will also be collected. This form will also capture data from the standard of care intraoperative transesophageal echocardiogram detecting intra-cardiac thrombi and/or endothelial disruptions on the interior of the aorta.

Epi-aortic Scan

Initial surgical intervention before cannulation and after decannulation

Epi-aortic scanning will be used to assess atheroma burden prior to cannulation. After the cannula is removed, epi-aortic scanning will be used to determine the presence or absence of aortic lesions.

POST-RANDOMIZATION DATA COLLECTION

Study Visits

- Peri-operative
- 1 and 3 days post procedure
- 7 (± 3) days post procedure
- 30 (± 7) days post procedure
- 90 (± 7) days post procedure

Diffusion-Weighted Imaging

At 7(± 3) days post procedure

Patients will undergo a diffusion-weighted 1.5 or 3.0 T MRI to detect brain lesions.

Hospitalizations

Index hospitalization and event driven

For all patients the index (baseline) hospitalization and all subsequent hospital admissions (for any reason) must be reported on the Hospitalization form. This form collects limited information about hospital procedures, length of stay, days in intensive care, and discharge, if applicable, as well as patient condition and disposition for each hospitalization.

Medications

At 7(± 3), 30 (± 7), and 90 (± 7) days post procedure and event-driven

All cardiovascular medications will be recorded at each study visit and also as indicated at the time of associated adverse events. All analgesics and psychopharmacological medications will be collected at Day 7 (± 3).

Physical Examination
At 7(± 3) and 90 (± 7) days post procedure
In this limited physical examination, vital signs and cardiopulmonary examination will be captured.

Neurocognitive Testing
At 90 (± 7) days post procedure
Cognitive performance will be assessed using the following battery of tests: Hopkins Verbal Learning Test; Trailmaking Tests A and B; MCG Complex Figures; Digit Span; Digit Symbol Substitution Test; and COWA Verbal Fluency Test.

Modified Rankin Scale
At 30 (± 7) and 90 (± 7) days post procedure
The mRS will be administered by a neurology trainee or study coordinator trained in the mRS.

NIH Stroke Scale
At 1, 3, 7(± 3), 30 (± 7) and 90 (± 7) days post procedure and within 24 hours after a neurological dysfunction adverse event
The NIHSS will be administered by a neurology trainee or study coordinator trained in the NIHSS.

CAM Assessment
At 1, 3, and 7 (± 3) days post procedure
The 3D-CAM (or CAM-ICU if the patient is intubated) will be administered by a neurology trainee or study coordinator trained in the 3D-CAM and CAM-ICU.

Barthel Index
At 30 (± 7) and 90 (± 7) days post procedure
The Barthel Index will be administered by a neurology trainee or study coordinator trained in the Barthel Index.

Quality of Life
At 90 (± 7) days post procedure
The SF-12v2 questionnaire will be completed by the patient to assess quality of life.

Depression
At 90 (± 7) days post procedure
The GDS will be administered by study staff trained to administer the GDS.

Event Driven Data Collection
Adverse Events
Event Driven
Detailed information regarding adverse events will be recorded at the time an adverse event becomes known. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All adverse events will be recorded until the patient completes the trial.

Laboratory Assessment
Event Driven
Laboratory values will be collected as needed when relevant to adjudication of adverse events.

- Hematology, including white blood cell *($10^3/\mu l$)*, Hemoglobin *(g/dl)*, Hematocrit *(%)*, Platelet count *($10^{3P}/\mu l$)*

- Coagulation profile, including prothrombin time (PT/sec), partial thromboplastin time (PTT/sec), International Normalized Ratio (INR)
- Blood chemistries, including sodium *(mM/L)*, potassium *(mM/L)*, blood urea nitrogen *(*BUN, *mg/dl)*, creatinine *(mg/dl)*
- Liver function tests, including total bilirubin *(mg/dl)*, alanine aminotransferase (ALT, *U/L)*, aspartate aminotransferase (AST, *U/L)*, albumin *(g/dl)*.

Missed Visit Assessment
Event Driven
If a patient is unable to return for follow-up before the closure of a study visit window, a missed visit assessment that captures the reason for missing the visit must be completed.

Mortality
Event Driven within 24 hours of knowledge of event
The investigator will record the date of death, immediate cause of death, primary underlying cause of death, notation of autopsy being performed, and clinical narrative of the event.

Study Completion/Early Termination
Event Driven
This form records the date and reason for study completion or early termination. The anticipated reasons for a patient to be withdrawn from this study are either the patient's request or at the physician's discretion, details of which will also be documented on this form.

Investigator's Statement
End of study
The PI will review all of the electronic case report forms (eCRFs) and patient summaries. His or her electronic signature attests to the accuracy and completeness of the data collected.

DATA MANAGEMENT

All study data will be entered in the web-based electronic data capture (EDC) system (specified in detail in the Operations Manual). Study personnel requiring access will have their own Login/Password. Access to clinical study information will be based on individuals' roles and responsibilities. The application provides hierarchical user permission for data entry, viewing, and reporting options. For optimum security, the system operates Secure Socket Layer (SSL) 128-bit encryption protocol over Virtual Private Networks (VPN). This application is designed to be in full compliance with International Conference on Harmonization and Good Clinical Practices (ICH-GCP), the FDA's Code of Federal Regulations (CFR) Number 21 Part 11 Electronic Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials, and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Quality Assurance
The data quality assurance tool has been designed as an automatic feature of the EDC system. When a form is submitted the system conducts instantaneous validation and cross-form validation checks. A query is generated and sent to the site coordinator electronically so that data may be verified and corrected. All changes made to a form are stored in an audit log.

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data and/or values that are outside the range of what is typically

considered to be physiologically possible). Monitors will enter these queries through the EDC system for site coordinators to either correct or verify.

Monitoring

The DCC monitoring team employs a risk-based approach to centralized and on-site monitoring. This approach focuses efforts on the most crucial data and process elements to allow for more efficient monitoring practices while maintaining the quality of the overall study conduct. Through the combination of centralized and on-site monitoring, instantaneous electronic validation via the EDC system, and visual cross-validation by the InCHOIR monitors to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

The centralized, or remote, monitoring of clinical trial data via the EDC is performed with a focus on safety, study endpoints, data completion and data outliers. DCC monitors will remotely monitor source documentation, study logs including the Informed Consent Log, the Protocol Violation/Deviation Log and the Serious Adverse Event/Safety Report Log periodically to ensure that the sites are adhering to the study protocol and procedures. In collaboration with the DCC data management team, the monitors will create and utilize reports outlining data completeness and timeliness, missing and outlier values as well as cross form consistency validations to generate queries and optimize reconciliation of data. This process significantly increases the efficiency of monitoring both remotely and while on site.

The DCC will conduct on-site monitoring visits after enrollment begins approximately once each year for every clinical site depending on site enrollment for the duration of the study. Copies of all source documents must be kept in the patient source binders at each site for review by the monitors.

The monitors will review the source documents to determine whether the data reported in the EDC system are complete and accurate. They will also verify that all adverse events exist on the source documents, are consistent with the protocol, and are documented in the appropriate format. Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission reports, consult notes, radiology reports, lab reports, clinic records, and other study-related notes. The study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

The monitors will also confirm that the regulatory binder is complete and that all associated documents are up to date. The regulatory binder should include all revisions of the protocol and informed consent, IRB/REB roster, IRB/REB approvals for all of the above documents, IRB/REB correspondence, investigator's agreements, delegation of authority log, CVs of all study personnel, institutional HIPAA certificates, monitor site visit log, telephone contact log, and correspondence with the DCC.

The monitor will verify a minimum of the following variables for all patients: initials, date of birth, sex, signed informed consent, eligibility criteria, date of enrollment, adverse events, and mortality. These data will be 100% source data verified. All other data collection will be monitored as indicated by the data completeness and accuracy at each clinical site.

If problems are identified during the monitoring visit (e.g., poor communication with the DCC, inadequate or insufficient staff to conduct the study, missing study documents, etc.), the monitor will assist the site in resolving the issues. Some issues may require input from the Steering Committee or the PI as well as the sponsor.

Given the combination of approximately yearly on-site monitoring and ongoing monitoring using the EDC system that includes instantaneous electronic validation and visual cross-validation to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

ANALYTICAL PLAN

General Design Issues

This study is a prospective, multi-center, single blind, parallel-group randomized clinical trial comparing each of two embolic protection devices to a control. While randomization is expected to include all three arms from trial initiation to completion, our design allows for staggered introduction of embolic protection devices. More generally, the similarity of embolic protection devices in terms of how they are used, the patients for whom they are indicated, and their expected benefit allows flexibility for introducing additional devices, when they are cleared or approved by the governing regulatory agency (e.g., FDA or Health Canada), into an ongoing trial evaluating one or more embolic protection devices.

Endpoint assessment will be blind to treatment strategy. Enrolled patients will undergo open aortic valve replacement and will be randomized to one of two embolic protection devices in the operating room or to a standard cannula. The trial's aim is to evaluate the extent to which the embolic protection devices provide neuroprotection, defined as freedom from CNS infarction at 7 (± 3) days post procedure. Given that the relationship between radiologic evidence of brain infarction and long-term neurofunctional outcomes is unclear, there is no planned interim analysis or early stopping boundary for efficacy.

Sample Size

Patients will be randomized with equal allocation into one of two embolic protection device groups and one control group. A sample size of 165 patients in each group provides 90% power to detect a relative 35% reduction in the incidence of post-operative CNS infarcts for patients treated with either device from an assumed 50% rate among control patients. Power is based on a 0.05 level two-sided chi-squared test. No adjustment to the Type I error rate will be made for the two planned comparisons as they are separate comparisons of each device treatment group to a shared control group. Note that if device initiation is staggered, more than 165 control patients will be required in total to ensure that 165 control patients are available for the comparison to the late-enrolling embolic protection device arm. Therefore, the total sample size will need to be at least 495 patients; additional patients, equal to the number of patients randomized to control prior to inclusion of the second device, will be randomized in this trial. As such, given our assumptions about the maximum difference between initiation of devices, as many as 535 patients may need to be randomized.

Randomization Design and Procedure

Patients will be randomized to use of either embolic protection device or standard cannula. Randomization will be stratified by procedure (isolated versus combined procedure), and by clinical center. A random permuted block design will be employed with blocks of size 3, 6, or 9 randomly chosen.

Data Analysis

Primary Analysis

The primary analysis will compare the incidence of CNS infarct between groups using a two-tailed 0.05 level chi-squared test. Death within 7 days is included as a treatment failure. The analysis will adhere to the intention to treat principle, with missing outcome data imputed using distance-aided selection of donors as described in Siddique and Belin (Siddique and Belin 2008). This imputation approach is an iterative hot-deck multiple imputation, that does not require assuming ignorable missing data. Predictive mean matching is used to estimate missing data by regressing observed outcomes on a set of observed covariates. Missing data are imputed based on "similar" cases. An approximate Bayesian bootstrap (ABB) (Rubin and Schenker 1986; Demirtas, Arguelles et al. 2007) will be used to incorporate parameter uncertainty into the hot-deck imputation models. An ignorable ABB draws observed cases at random for imputation; under non-ignorable assumptions, probability weights are used in the bootstrap based on a "similarity" index. Covariates will include age, sex, group, neurocognition, and measures of morbidity;

all selected prior to unmasking outcome data. Our primary analysis will employ the approach assuming a non-ignorable missing data mechanism; additional sensitivity analyses will be performed assuming missing data are ignorable.

An important secondary objective of this trial is to develop a better understanding of the relationship between radiographic evidence of stroke and clinical stroke (i.e., a confirmed diagnosis by a neurologist) and also with neurocognitive outcomes. Radiographic evidence of stroke is based on both the number and volume of emboli. The relationship between number and volume of emboli and clinical stroke will be determined using logistic regression models. Additional analyses using receiver operating characteristic curve methods will assess to what extent radiographic evidence can accurately classify patients diagnosed with stroke. Agreement between the presence of any radiographic lesions and clinical stroke will be estimated using the relative risk and its associated 95% confidence interval. Linear regression will be used to quantify the relationship of each radiographic measure (number, volume, and presence of any lesions) to each neurocognitive outcome.

Adherence to Imaging Endpoint Assessment
As in any clinical trial, having a high completion rate of the primary endpoint (in this case DWI MRI) is critical. We assume that patient refusals will be few as the primary endpoint assessment is at 7 (± 3) days post-surgical procedure. We believe that the burden to the patient should be minimal (in terms of travel back to the clinical site) as the primary endpoint assessment, which includes a flexible window for completion, will be done during the index hospitalization. The timing of the primary endpoint assessment will also allow most patients to have their pacer wires removed. We anticipate 10-15% missing data.

Secondary Analysis
A secondary sensitivity analysis will be conducted to look at the treatment effect on subgroups of valve type (i.e. sutureless, mechanical, or bioprosthetic) in the same manner as the primary outcome.

Analysis of Secondary Endpoints
Clinical Composite Endpoint (Mortality, Clinical Stroke, and Acute Kidney Injury)
The proportion of patients who have experienced clinical stroke, acute kidney injury, or died within 30 days will be compared by a chi-squared test of the equality of two proportions.

Volume of Brain Lesions
Volume of lesions is expected to be highly skewed, with a preponderance of zero values and a few very large outlying values. The most informative analysis of volume may depend on the observed distribution of values. Our approach will be to pre-specify the Wilcoxon-Rank Sum test as the primary analysis of group differences, and to possibly augment this analysis with one or more additional distribution free approaches, such as a randomization test.

Number of Brain Lesions
Differences between randomization arms in the number of brain lesions detected based on radiographic assessment 7 (± 3) days post procedure will be assessed using a zero-inflated Poisson regression model.

Neurocognitive Function
Neurocognitive outcomes for each of the six domain tests will be standardized using the means and standard deviations observed in the overall sample and combined within cognitive domains using weights that will be defined by the CTSN Neurocognitive Core Lab. Differences in the scores for each domain at baseline and 90 (± 7) days post procedure will be compared between randomization arms based on an analysis of covariance. Analysis of neurocognitive function will be adjusted for depressive symptoms as measured by the GDS.

Delirium
The incidence of delirium as determined by the CAM assessment at each time point (pre-operatively and at days 1, 3, and 7 (± 3)) will be compared between randomization groups using the chi-squared test of the equality of two proportions.

Serious Adverse Events, Adverse Events and Mortality
The proportion of deaths between randomization groups at 90 days post procedure will be compared by a chi-squared test of the equality of two proportions. Time to death will be described by Kaplan-Meier curves and differences between randomization groups will be assessed via the log-rank test.

Other Adverse Events
The proportion of patients with aortic lesions after decannulation will be compared between treatment groups using a chi-squared test of the equality of two proportions. Differences in the incidence of individual adverse events and serious adverse events will be compared between randomization arms using Poisson regression. Exact 95% confidence intervals (based on the Poisson distribution) for the risk ratios for individual adverse events by treatment arm.

Hospitalization
Hospital length of stay and days in ICU
We will compare hospital length of stay and days spent in ICU between treatment groups using a Wilcoxon Rank-Sum test.

Readmissions
We will use Poisson regression models to compare the frequency and causes of readmissions between groups at both 30 and 90 days.

Quality of Life
Mean quality of life scores, as assessed by the SF-12v2 at 90 (± 7) days, will be compared between groups using a paired two-sample t-test.

Incidence of depression at day 90 (± 7) will be compared between randomization groups using the chi-squared test of the equality of two proportions.

Economic
Hospital resource utilization or hospital costs will be calculated by converting charges to costs using institution specific Ratio-of-Cost-to-Charges (RCCs). Institution-specific cost reports or administrative costing datasets (e.g., University Hospital Consortium data) will be used to calculate RCCs for each major resource category. Costing data will be compared by Student's t test after log transformation. Independent predictors of cost, including baseline factors, operative factors and postoperative events, will be determined by multivariate regression analysis.

Exploratory Analyses
All analyses described above will be repeated comparing arms receiving therapy with an embolic protection device to each other. These analyses are exploratory given that the planned sample size is unlikely to provide adequate power to detect meaningful differences.

Interim Analysis
We plan to perform a single interim analysis with respect to the primary endpoint to give the option of stopping early should results strongly favor one arm or the other. The proposed timing of this analysis is at 0.5 on the information scale, i.e., after one-half of patients (165) have undergone the primary endpoint assessment. The interim analysis will be performed as described for the final analysis, with separate comparisons of each embolic protection device group to its respective control group. A group sequential

procedure will be used to allow for flexibility in the number and timing of interim analyses should the DSMB choose to modify the proposed plan, or should accrual mitigate the usefulness of an interim look. We will use the Lan-DeMets approach, implementing an O'Brien-Fleming-type spending function that allots most of the type I error to the final look. The resulting critical values to be used for each analysis are 2.963 at the first interim analysis, 1.969 at the final analysis.

In addition to the ethical concern of continuing a trial that shows a clear benefit in favor of one treatment, there is also a corresponding ethical concern of continuing a trial that has little chance of ever showing a benefit of one treatment compared to the other. We propose that for each comparison of active device therapy compared to control, that comparison's conditional power, under the original alternative hypothesis, be computed at the interim look and that the DSMB use this to determine whether randomization be halted for futility. We propose that consideration be given to halting the trial for futility if, given the data up to the point of each interim analysis, the probability of detecting a relative 35% reduction (from 50% to 32.5%) in the incidence of clinical or radiographic CNS infarction in patients randomized to an embolic protection device, compare to those randomized to no protection device, is less than 20%.

We do not propose any a priori stopping criteria based on adverse events. The treatments in this trial are not experimental, and have well known adverse event profiles. Moreover, we believe that incident rates of adverse events and mortality must be interpreted along with information about the consistency of related measures, consistency across centers, data completeness, and any external factors including scientific developments that might impact patient safety. In addition to considering the data generated by this trial, the DSMB will consider all relevant background knowledge about the treatment of mitral regurgitation. The DSMB would be capable, and uniquely suited, to determine decisions for convening outside the schedule of meetings, and to determine decisions to suspend or terminate the trial. These decisions should be at the discretion of the DSMB alone. We therefore recommend that the DSMB should be responsible for defining its deliberative processes, including event triggers that would call for an unscheduled review.

In addition to the formal monitoring guidelines above, we propose to examine, at regular intervals determined in consultation with the trial's DSMB, the relationship between patient age and the incidence of primary outcomes in patients aggregated across all treatment groups. This examination (masked to the treatment the patient received) is proposed to monitor two details: (1) the relative incidence of primary endpoint events among randomized patients less than 65 years of age compared to those greater than or equal to 65 years of age, and (2) the proportion of randomized patients less than 65 years of age.

ORGANIZATION OF THE STUDY

This section describes the overall study organization. The study is conducted in the Cardiothoracic Surgical Trials Network (CTSN) clinical sites selected by NHLBI in collaboration with NINDS and CIHR. The trial is supported by NHLBI, NINDS, and CIHR. The following committees and institutions will be involved in the administration of the study.

Event Adjudication Committee (EAC)

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all adverse events and causes of mortality. The individuals who will serve on the committee are unaffiliated with the clinical sites and the DCC, and will be appointed by the DCC. The committee will consist, at least, of a cardiothoracic surgeon a cardiologist, and a neurologist. The EAC will meet every 6 months or as needed to review outcomes data for each subject enrolled.

Data and Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians, biostatisticians,

ethicists, neurologists and bioengineers who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC, or the clinical sites and will be appointed by the NHLBI. The DSMB will act in a senior advisory capacity to the DCC and the NHLBI regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events and mortality. They will communicate their findings directly with the DCC and the NHLBI. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

Data Coordinating Center (DCC)
A university-based DCC (InCHOIR) will collaborate with the Network Investigators. The DCC bears responsibility for monitoring interim data and analyzing the study's results in conjunction with the investigators and the sponsor. It will coordinate and monitor the trial and will administrate the DSMB and EAC.

MRI Core Lab
The MRI Core Lab, located at the University of Pennsylvania, is directed by Michel Bilello, PhD. All MRIs will be performed according to a standardized protocol (see Manual of Operations) and will be centrally analyzed.

Neurocognitive Core Lab
The Neurocognitive Core Lab, located at Duke University, is directed by Joseph Mathew, MD. The core lab will be responsible for training the clinical site personnel in administration of the specific tests. All neurocognitive tests will be scored centrally by the core lab.

Histology Core Lab
The Histology Core Lab, located at CV Pathology is directed by Renu Virmani, MD. The histology core lab will analyze the debris captured in the filters, including electron microscopy.

Executive Steering Committee
The CTSN Executive Steering Committee, with the assistance of the Protocol Development Committee (PDC), will provide the overall scientific direction for the study. The responsibilities of the Steering Committee are to: (a) maintain contact with study investigators to ensure high quality data collection; (b) approve and implement major protocol changes in response to advice from the DSMB; (c) collaborate in data analysis, interpretation, and publication; (d) establish criteria for authorship on all manuscripts, publications, and presentations that arise from the study.

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Appendix I: Neurocognitive Testing

HOPKINS VERBAL LEARNING TEST TRIAL INSTRUCTIONS
Trial 1
Say the following:

> **I am going to read a list of words to you. Listen carefully, because when I'm through, I'd like you to tell me as many of the words as you can remember. You can tell them to me in any order. Are you ready?**

- Repeat or paraphrase the instructions if necessary
- Read the words at the rate of approximately one word every 2 seconds
- If the individual does not spontaneously begin reporting words after the last word is read, say the following:

> **OK. Now tell me as many of those words as you can remember**

Record the responses verbatim (including repetitions and intrusions) in the Trial 1 column. When the individual indicates no more words can be recalled, proceed to Trial 2.

Trial 2
Say the following:

> **Now we are going to try it again. I am going to read the same list of words to you. Listen carefully, and tell me as many of the words as you can remember, in any order, including all the words you told me the first time.**

Use the same procedure as in Trial 1 to record the responses in the column for Trial 2. Then proceed to Trial 3.

Trial 3
Say the following:

> **I am going to read the list one more time. As before, I'd like you to tell me as many of the words as you can remember, in any order, including all the words you've already told me.**

Record the responses in the column for Trial 3 using the same procedure as in the previous trials.

NOTE: *Do not tell the respondent that recall of the words will be tested later*.

Delayed Recall Trial Instructions

After the 20 –25 minute delay, say the following:

> **Do you remember that list of words you tried to learn before?**

If the response is "No," remind the individual that you read the list three times and that he or she was asked to recall the words each time. Say the following:

> **Tell me as many of those words as you can remember.**

Delayed Recognition Trial Instructions

The delayed recognition (forced choice) trial is administered immediately after the Delayed Recall trial. Say the following:

> **Now I am going to read a longer list of words to you. Some of them are words from the original list, and some are not. After I read each word, I'd like you to say "Yes" if it was on the original list or "No if it was not.**

Read the words of the Delayed Recognition trial list in numerical order. Allow the individual as much time as needed to respond. You may use the prompt, **"Was horse on the list? Yes or no?"** The individual must give you a response for every word. If the individual is not sure, ask for a guess.

TRAIL MAKING TEST INSTRUCTIONS

Part A:
Give the subject a pencil and the test page and say: *"On this page are some numbers."* Point to some numbers. *"Begin at number 1"* Point to number 1. "*and draw a line from 1 to 2, "Point* to number 2. *"2 to 3,"* Point to 3. *"3 to 4,"* Point to 4. "*and so on, in order, until you reach the end."* Point to the circle marked "end". *"Draw the lines as fast as you can. Ready ------- Begin!"* If the subject completes the sample item correctly demonstrating his/her understanding say: *"Good! Let's try the next one."* Turn the paper over and give Part A of the test. If the person makes a mistake on sample A, point out the error and explain it.

The following explanations of mistakes serve as illustrations.
1. "You started with the wrong circle. This is where you start (point to number one)"
2. *"You skipped this circle (point to the circle the subject omitted). You should go from number 1* (point) *to 2* (point), *to 3* (point), *and so on, until you reach the circle marked "end"* (point)*."*

If the subject cannot complete Sample A, take his/her hand and guide the pencil, using the eraser end, through the trail. Then say: *"Now you try it."*

Return the pencil to the subject with the point down and say: *"Remember, begin at number 1 (point) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4) and so on, in order, until you reach the circle marked "end" (point). Do not skip around, but go from one number to the next in the proper order. Remember to work as fast as you can. Ready --- Begin!"*

If the subject succeeds this time proceed to Part A. If the subject still has difficulty, repeat the above procedure until the task is completed successfully or it becomes evident that the subject cannot do the task.

After the subject has completed Sample A, turn the paper over to Part A and say: *"On the page are numbers. Do this the same way. Begin at number 1 (point 1) and draw a line from 1 to 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), and so on, in order, until you reach the end (point). Remember to work as fast as you can. Ready ---Begin!"*

Using a stopwatch, start timing as soon as the instruction is given to begin. The examiner must watch the subject closely in order to catch any errors as soon as they are made. If the subject makes an error, call it to his/her attention immediately, return the subject's pencil to the last correct circle, and continue the test from that point. Do not stop timing while correcting the subject's error.

After the subject completes Part A, take the test sheet and record the time in seconds. Errors contribute to evaluation of performance principally by increasing the total performance time.

Trails (Part B):
Next, tell the patient: *"That's fine. Now we'll try another one."* Place the sample side of Part B on the table in front of the subject, in the same position as the sheet for Part A was placed. Point to the sample and say:

"On this page are some numbers and letters. Begin at 1 (point) and draw a line from 1 to A" (Point to A) *"A to 2,"*(Point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"3 to C"* (point to C**),** *"and so on, in order, until you reach the end"* (point to the circle marked "end").

Then say: *"Remember, first you have a number"* (point to 1), *"then a letter"* (point to A), *"then a number"* (point to 2), *"then a letter"* (point to B), "*and so on. Draw the lines as fast as you can. Ready---Begin!"*

If the subject completes the sample B correctly say: *"Good! Let's try the next one."* Proceed immediately to Part B. If the subject makes a mistake on sample B, point out the error and explain why it is incorrect.

The following explanations of mistakes serve as illustrations:

1. *"You started with the wrong circle. This is where you start (point to number 1)"*
2. *"You skipped this circle"* (point to the circle the subject omitted). "*You should go from 1"* (point to 1) *"to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3) *"and so on until you reach the circle marked 'end'*. (point)

If the subject cannot complete Sample B, take his/her hand and guide the pencil, using the eraser end, through the circles. Then say: *"Now you try it. Remember, you begin at number 1"* (point) *"and draw a line from 1 to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"and so on until you reach the circle marked "end" (point). "Ready --- Begin!"*

If the subject succeeds this time, go on to Part B. If not repeat the procedure until the task is performed successfully or it becomes evident that the subject cannot do the task.

After the subject has completed the sample, turn the paper over to Part B and say:
"On this page are both numbers and letters. Do this the same way. Begin at number 1" (point to 1) *"and draw a line from 1 to A"* (point to A), *"A to 2"* (point to 2), *"2 to B"* (point to B), *"B to 3"* (point to 3), *"3 to C"* (point to C), *"and so on, in order, until you reach the end"* (point to the circle marked "end*"). "Remember, first you have a number"* (point to 1), *"then a letter"* (point to A), "*then a number"* (point to 2), *"then a letter"* (point to B), *"and so on. Do not skip around, but go from one circle to the next in the proper order. Draw the lines as fast as you can. Ready ---Begin!"*

Using the stopwatch, start timing as soon as the subject is told to begin. Remember to be alert for mistakes. If the subject makes an error, point it out immediately, return the subject to the last correct circle, and continue the test from that point. Do not stop timing.

After the subject completes Part B, take the test sheet and record the time in seconds. Errors contribute to the evaluation of the performance principally by increasing the total performance time.

Scoring
Part A and Part B are scored separately. The score for each part is the number of seconds required to complete the task.

DIGIT SPAN INSTRUCTIONS
Digit Span (Wechsler Adult Intelligence Scale - Third Edition)

Administration Rules:
Administer Digits Backward even if participant scores a 0 on Digits Forward.

Read digits at a rate of 1 per second in a loud, even voice, dropping the tone of your voice at the end of the string of digits, as if you were ending a sentence.

Write down the numbers that the participant says, in the order he/she repeats them. Do not let the participant know whether or not the responses are correct.

The participant is allowed to change his/her response. If the participant changes the response on one of the items, write 'participant changed mind' next to the correction.

Digits Forward: State to the participant:
"I am going to say some numbers. Listen carefully, and when I stop, say them right after me."

Digits Backward: State to the participant:
"Now I am going to say some numbers, and this time when I stop I want you to say them backward. For example, if I say 7-1-9 what would you say?"

If participant says 9-1-7, say ***"That's right."*** and continue with test

If participant is incorrect, **say** ***"No, you would say 9-1-7. I said 7-1-9, so to say it backward, you would say 9-1-7. Now try these numbers. Remember, you are to say them backward. 3-4-8."*** Do not provide any assistance on this example or any of the items.

Whether or not the participant responds correct (i.e., 8 – 4 – 3), proceed to Trial 1 of Item 1.

Scoring:
Each item is scored 0, 1, or 2 points as follows:

- 2 points if the participant passes both trials
- 1 point if the participant passes only one trial
- 0 points if the participant fails both trials

Discontinuation Rule:
Digits Forward and Digits Backward
Discontinue test when participant obtains a trial score of 0 on both trials of any item.

DIGIT SYMBOL SUBSTITUTION TEST INSTRUCTIONS
DIGIT SYMBOL SUBSTITUTION TEST (Wechsler Adult Intelligence Scale - Third Edition)

- A smooth drawing surface must be provided. If the table has a rough surface, the Record Form should be placed on a clipboard, a piece of cardboard, or another flat surface.
- To introduce the subtest, say:
  In this section, I'm going to ask you to copy some symbols.
- If examinees ask what they should do if they make a mistake, encourage them to continue to work as fast as they can. However, do not discourage examinees from making spontaneous corrections unless they do so repeatedly and it impedes their performance.
- If, after completing a row, an examinee to start at the beginning of the row and not to skip any.

Item Instructions
Turn to the Digit Symbol-Coding page. Hand the examinee a pencil without an eraser, point to the key above the test items, and say:

Look at these boxes. Notice that each has a number in the upper part and a special mark in the lower part. Each number has its own mark.

Point to 1 and its mark in the key, then 2 and its mark. Then point to the seven squares located to the left of the heavy black line and say:

Now look down here where the squares have numbers in the top part but the squares at the bottom are empty. In each of the empty squares, put the mark that should go there. Like this:

Point to the first Sample Item, then point back to the key to show its corresponding mark, and say:

Here is a 2; the 2 has this mark. So I put it in this empty square, like this:

Write in the symbol. Point to the second Sample Item and say:

Here is a 1; the 1 has this mark (point to the second Sample Item, then to the mark below the 1 in the key**), so I put it in this square.**

Write in the symbol. Point to the third Sample Item and say:

This number is a 3; the 3 has this mark (point to the third square and to the mark below the 3 in the key)**. So I put in the square** (write in the symbol)**.**

After marking the first three Sample Items, say:

Now you fill in the squares up to this heavy line.

If the examinee makes an error on any of the Sample Items, correct the error immediately and review the use of the key. Continue to provide help if needed. Do not proceed with the subtest until the examinee clearly understands the task. When the examinee completes a Sample Item correctly, offer encouragement by saying **Yes** or **Right.** When all the Sample Items have been completed, say:
Now you know how to do them. When I tell you to start, you do the rest of them.
Point to the first square to the right of the heavy line and say:

Begin here and fill in as many squares as you can, one after the other without skipping any. Keep working until I tell you to stop. Work as quickly as you can without making any mistakes.

Sweep across the first row with your finger and say:

When you finish this line, go on to this one.

Point to first square in the second row. Then point to the heavy black line and say:
Go ahead.
*****Begin timing.**

If the examinee omits an item or starts to do only one type (e.g., only the 1's), say:

Do them in order. Don’t skip any.

Point to the first item omitted and say:

Do this one next.

Provide no further assistance except to remind the examinee to continue until instructed to stop. At the end of 120 seconds, say: **Stop**

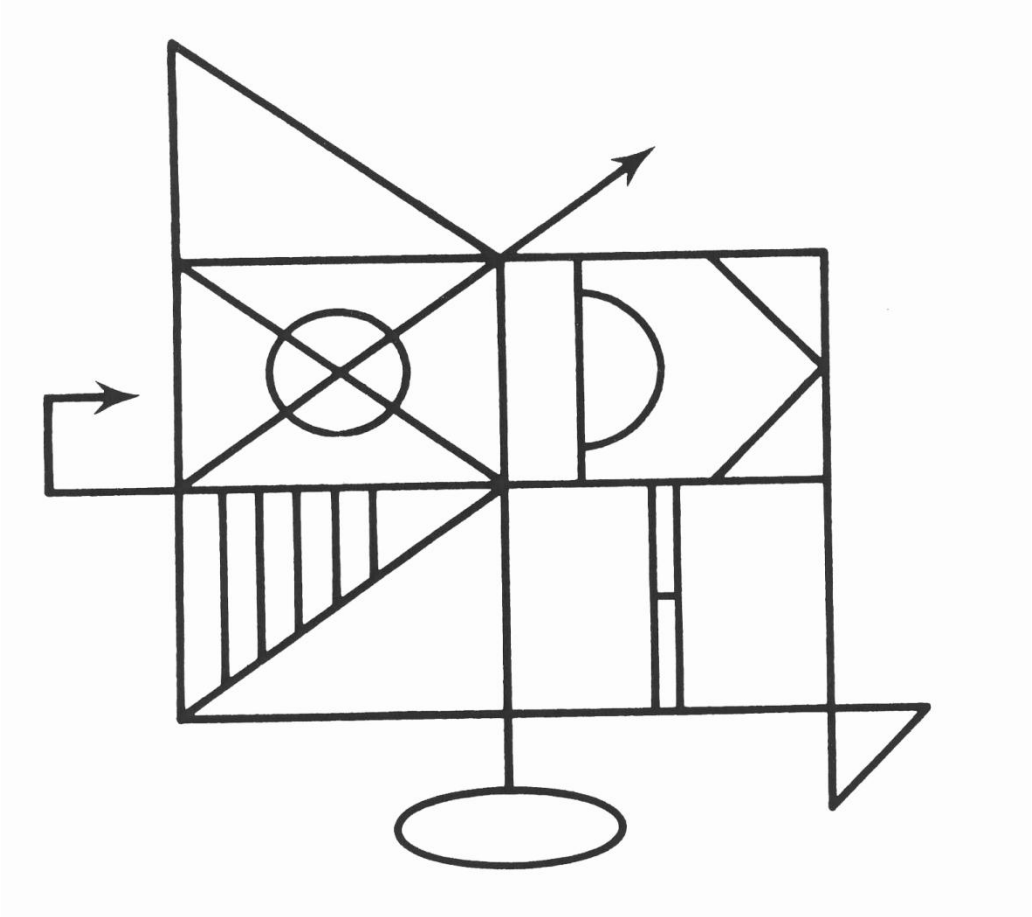
MEDICAL COLLEGE OF GEORGIA (MCG) COMPLEX FIGURES TEST INSTRUCTIONS
MCG Complex Figures (A compendium of neuropsychological tests (3rd Edition); Strauss E, Sherman EMS, Spreen O. New York, USA: Oxford University Press, 2006: 1216

Present figure to participant and ask participant to replicate it as precisely as possible on an 8.5 in. by 11 in. sheet of paper. Once completed, remove the figure. Ask the participant to reproduce the figure following a 3 minute delay (immediate recall) and a 30 minute delay (delayed recall). There are no time limits for all figural reproductions.

SCORING:
Consider each of the eighteen units separately. Appraise accuracy of each unit and relative position within the thole of the design. For each unit count as follows:

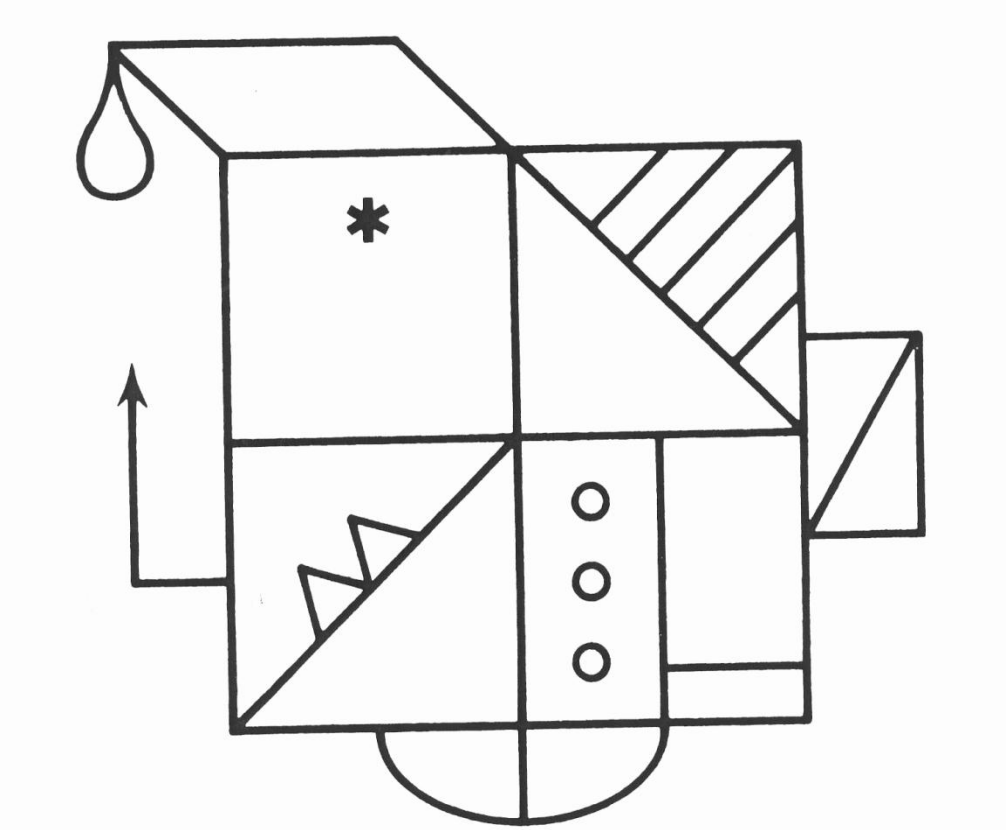
Correct, placed properly	2 points
Correct, placed poorly	1 point
Distorted or incomplete but recognizable, placed properly	1 point
Distorted or incomplete but recognizable, placed poorly	1/2 point
Absent or not recognizable	0 points
Maximum total points	36 points

FIGURE 1:



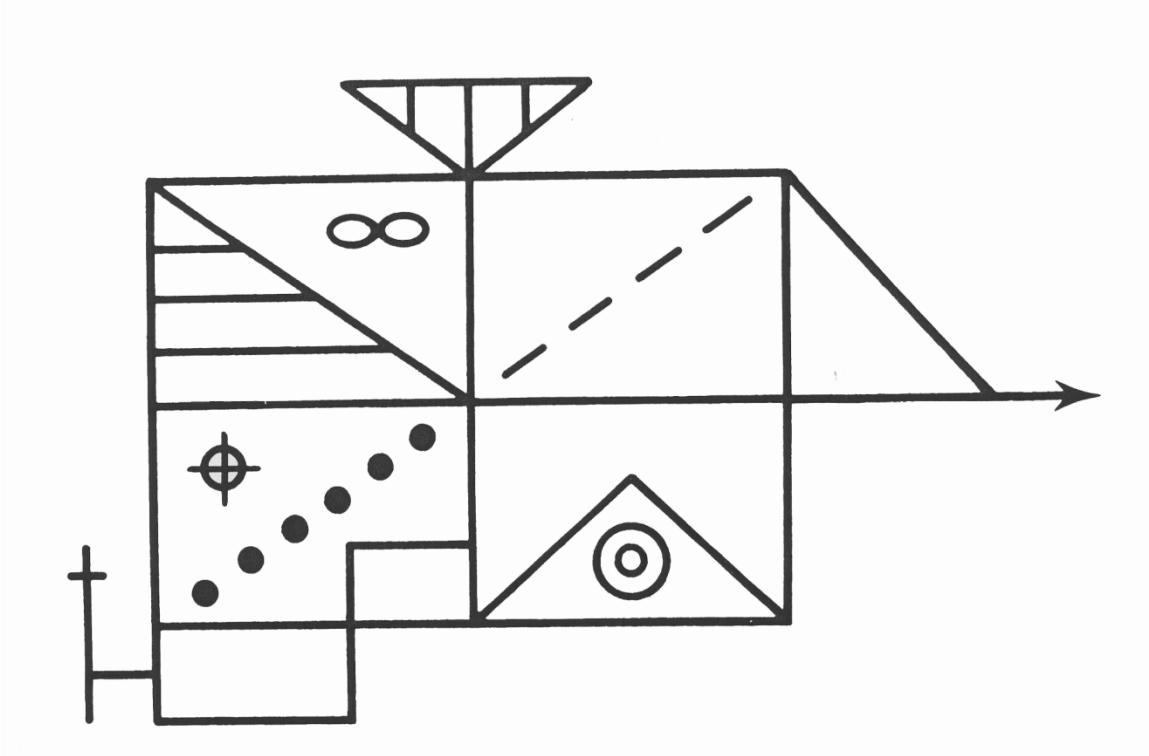
1. Large rectangle
2. Vertical midline of 1
3. Horizontal midline of 1
4. Small triangle on right corner of 1
5. Oval and attaching line at the bottom of 1
6. Bent arrow to the left of 1
7. Triangle above left upper quadrant of 1
8. Tilted arrow at top of 1
9. Diagonal in upper left quadrant of 1
10. Second diagonal in upper left quadrant of 1
11. Circle in upper left quadrant of 1
12. Diagonal in lower left quadrant of 1
13. Five vertical lines extending above 12
14. Vertical lines and horizontal connection (“H”) in lower right quadrant of 1
15. Vertical line in right upper quadrant of 1
16. Semicircle attached to the right of 15
17. Diagonal line at upper right corner of 1
18. Diagonal line extending from 17 to 3

FIGURE 2:



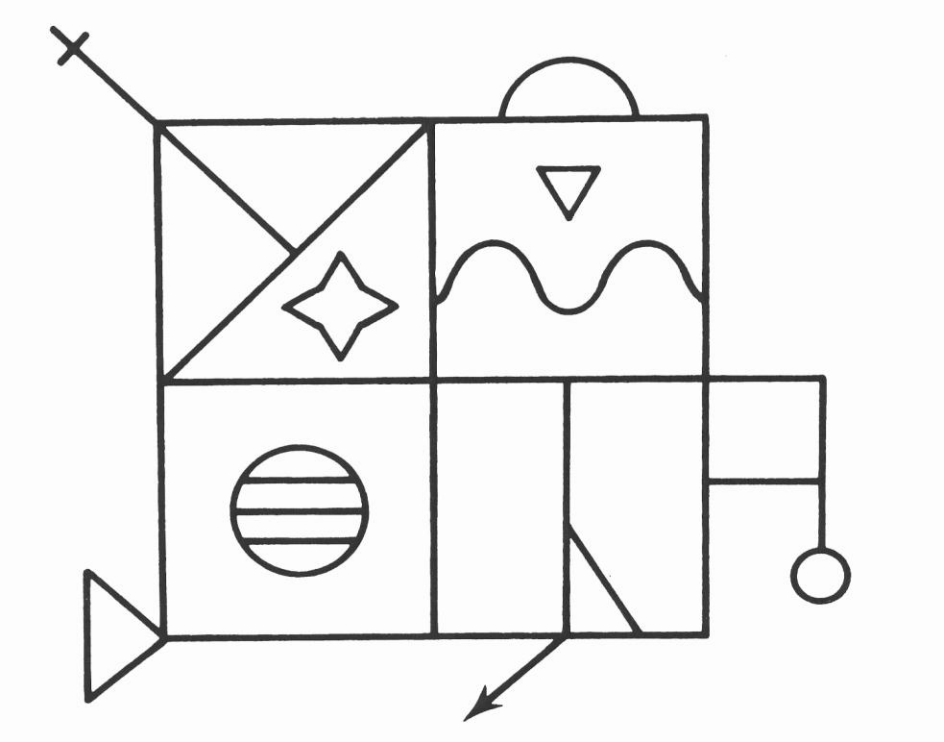
1. Large square
2. Vertical midline for 1
3. Horizontal midline for 1
4. Asterisk in the upper left quadrant of 1
5. Diagonal in the lower left quadrant of 1
6. Two triangles attached to 5
7. Three circles in the lower right quadrant of 1
8. Vertical midline in the lower right quadrant of 1
9. Horizontal line to the right of 8
10. Diagonal line in the upper right quadrant of 1
11. Five diagonal lines perpendicular to 10
12. Small rectangle to the right of 1
13. Diagonal line in 12
14. Semicircle at the base of 1
15. Vertical line in 14
16. Angled arrow to the left of 1
17. Parallelogram above 1
18. Teardrop attached to 17

FIGURE 3:



1. Large rectangle
2. Vertical midline of 1
3. Horizontal midline of 1
4. Diagonal line in left upper quadrant of 1
5. Three horizontal lines extending to 4
6. Infinity sign in left upper quadrant of 1
7. Circle and cross in lower left quadrant of 1
8. Six diagonal dots in lower left quadrant of 1
9. Small rectangle in lower left quadrant of 1
10. Small rectangle extending from bottom of 1
11. Cross attached to 10
12. Right angle in lower right quadrant of 1
13. Two concentric circles placed under 12
14. Four dashed lines in upper right quadrant of 1
15. Triangle atop 1
16. Three vertical lines in 15
17. Triangle to the right of 1
18. Arrow attached to the right of 17

FIGURE 4:



1. Large square
2. Vertical midline of 1
3. Horizontal midline of 1
4. Rectangle to the right of 1
5. Circle with stem attached to 4
6. Angled arrow at bottom of 1
7. Small triangle outside lower left corner of 1
8. Cross outside of upper left corner of 1
9. Semicircle on top of 1
10. Diagonal line in the upper left quadrant of 1
11. Perpendicular line to 10
12. Star in the upper left quadrant of 1
13. Circle in the lower left quadrant of 1
14. Three horizontal lines inside of 13
15. Small triangle in upper right quadrant of 1
16. Sine wave in upper right quadrant of 1
17. Vertical midline of the lower right quadrant
18. Diagonal line extending to right of 17

CONTROLLED ORAL WORD ASSOCIATION (COWA)

Description

This is an oral fluency test in which the subject is required to make verbal associations to different letters of the alphabet by saying all the words which he or she can think of beginning with a given letter. Three letters of progressively increasing associative difficulty are presented successively as stimuli. The difficulty level of each letter was defined in terms of the relative frequency of words beginning with that letter found in standard dictionaries of the English language.

Form A: The letter S (frequency rank =1) is used to demonstrate the test to the patient. The first letter in the test is C (frequency rank =2). The second letter is F (frequency rank = 10). The third letter is L (frequency rank =14). This form has been standardized for clinical use.

Form B: The letter S is used to demonstrate the test. The first letter in the test is P (frequency rank =3). The second letter is R (frequency rank =9). The third letter is W (frequency rank =16). This form has not been independently standardized but its correlation with Form A has been assessed. The correlation coefficient between Forms A and B in a sample of 54 normal subjects, who were given both forms in counterbalanced order, was .82. Mean scores for Forms A and B were 36.9 and 38.1 respectively, the difference between the means being non-significant.

Administration

Instructions: "I AM GOING TO SAY A LETTER OF THE ALPHABET AND I WANT YOU TO SAY AS QUICKLY AS YOU CAN ALL THE WORDS THAT YOU CAN THINK OF WHICH BEGIN WITH THAT LETTER. YOU MAY SAY ANY WORDS AT ALL, EXCEPT PROPER NAMES SUCH AS THE NAMES OF PEOPLE OR PLACES. SO YOU WOULD NOT SAY *ROCHESTER* OR *ROBERT*. ALSO DO NOT USE THE SAME WORD AGAIN WITH A DIFFERENT ENDING, SUCH AS *EAT* AND *EATING*. FOR EXAMPLE OF I SAY S, YOU WOULD SAY *SON, SIT, SHOE* OR *SLOW*. CAN YOU THINK OF OTHER WORDS BEGINNING WITH THE LETTER S?"

Wait for the subject to give a word. If successful, indicate that he or she is performing correctly and ask for another word beginning with the letter S. If he or she gives a second appropriate word, indicate that the subject is performing correctly and proceed to the test itself. If an inappropriate word is given on either occasion, correct him or her and repeat the instructions. If the subject then succeeds, proceed to the test. If he or she fails to respond, repeat the instructions. If it becomes clear that the subject does not understand the instructions or cannot associate, terminate the procedure.

If the subject has succeeded in giving two appropriate words beginning with the demonstration letter, say, "THAT IS FINE. NOW I AM GOING TO GIVE YOU ANOTHER LETTER AND AGAIN YOU SAY ALL THE WORDS BEGINNING WITH THAT LETTER THATN YOU CAN THINK OF. REMEMBER, NO NAMES OR PLACES, JUST ORDINARY WORDS. ALSO, IF YOU SHOULD DRAW A BLANK, I WANT YOU TO KEEP ON TRYING UNTIL THE TIME LIMIT IS UP. YOU WILL HAVE ONE MINUTE FOR EACH ONE. THE FIRST LETTER IS C."

Allow one minute. If the subject discontinues before the end of the time period, encourage him or her to try to find more words. If silent for 15 seconds, repeat the basic instruction and the letter. Not extension on the time limit is made in the event that the instruction is repeated in the course of the association.

Continue the test with the letters F and L, allowing one minute for each. If the patient produces one or more questionable responses (e.g. *frank, ford,* which could represent a proper name), the associations

should simply be recorded and he or she should not be interrupted. However, at the end of the one minute period of association, the patient should be asked what he or she meant by the responses.

Recording and Scoring

The Record Sheet provides numbered lines on which the subject's responses can be entered. If the speed of word production is too fast to permit verbatim recording, a"+" should be entered to indicate a correct response. However, all incorrect responses should be recorded verbatim.

The instructions include a specific prohibition against giving different forms of the same word. Hence, inflections of the same word (e.g., *eat-eating; eat-ate; mouse-mice; eat-eats; loose-loosely; eat-eaten*) are not admissible responses. Subjects often give both a verb and the substantive derived from the verb or adjective (e.g. *fun-funny; sad-sadness*). These are not admissible responses. On the other hand, if the substantive refers to a specific object (e.g., *clap-clapper; foot-footstool; hang-hanger*) it would be counted as an admissible response.

Repetition of a word having more than one meaning (e.g., *foot; can; hand*) is acceptable if the subject definitely indicates the alternative meaning. Slang terms are admissible if in general use. Foreign words (e.g., *passé; lasagna; pasta; Lebensraum*) are admissible if they can be considered part of the English lexicon, the criterion being their listing in a standard English dictionary.

The total number of acceptable responses for the three letters constitutes the patient's raw score on the test.

Appendix II: Modified Rankin Scale (mRS)

Instructions: Assessment should be completed by a certified evaluator.

1. Check the most single representative score
2. Screen: Score should reflect patient status prior to symptom onset of the present stroke.
3. Follow-up: Score should reflect patient status at the time of the exam
4. "Assistance" is defined as needing help from another person for mobility or other usual activities.

☐ 0= No symptoms at all

☐ 1= No significant disability, despite symptoms; able to carry out all usual duties and activities

☐ 2= Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance

☐ 3= Moderate disability; requiring some help, but able to walk without assistance

☐ 4= Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

☐ 5= Severe disability; bedridden, incontinent and requiring constant nursing care and attention

Appendix III: NIH Stroke Scale (NIHSS)

The NIH Stroke Scale (NIHSS) is a standardized neurological examination intended to describe the neurological deficits found in large groups of stroke patients participating in treatment trials. The instructions reflect primary concern for reproducibility. The purpose of this form is to collect data representing the baseline stroke status of each participant and the stroke status at different exam time frames of the trial. Please Note: The NIH Stroke Scale must be administered by a Stroke Neurologist or trained site coordinator. The coordinator and the neurologist must be trained and certified in the NlH Stroke Scale.

This is also part of the neurological exam conducted for suspected stroke during follow-up.

Date and time of form completion. Record the date (dd/mm/yyyy) and time (24-hr clock) the form was completed.

Directions: Indicate one box for each category. If any item is left untested, a detailed explanation must be clearly written on the form in the comment section.

Level of Consciousness

Three items are used to assess the patient's level of consciousness. It is vital that the items be asked in a standardized manner, as illustrated in the Stroke Scale training tape. Responses must be graded based on what the patient does first. Do not give credit if the patient corrects himself/herself and do not give any clues or coaching.

1a. Level of Consciousness (LOC)

Ask the patient two or three general questions about the circumstances of the admission. Also, prior to beginning the scale, it is assumed that the examiner will have queried the patient informally about the medical history. Based on the answers, score the patient using the 4-point scale on the Stroke Scale form. Remember not to coach. A score of 3 is reserved for the severely impaired patient who makes, at best, reflex posturing movements in response to repeated painful stimuli. If it is difficult to choose between a score of 1 or 2, continue to question the patient about historical items until you feel comfortable in assessing level of consciousness.

1b. LOC Questions

Ask the patient "how old are you now" and wait for a response. Then ask "what month is it now" or "what month are we in now". Count the number of incorrect answers and do not give credit for being "close". Patients who cannot speak are allowed to write. Do not give a list of possible responses from which to choose the correct answer. This may coach the patient. Only the initial answer is graded. This item is never marked "untestable". (Note: On Certification Tape #1 an intubated patient was given a series of responses from which to choose, but the score for this patient would still be 1.) Deeply comatose (1a=3) patients are given a 2.

1c. LOC Commands

Say to the patient "open your eyes...now close your eyes" and then "Make a fist...now open your hand". Use the non-paretic limb. If amputation or other physical impediment prevents the response, use another suitable one step command. The priming phrase is not scored, and these are used only to set the eyes or hand in a testable position. That is, the patient may be asked first to open the eyes if they are closed when you begin the test. Scoring is done on the second phrase "close your eyes". Count the number of incorrect responses and give credit if an unequivocal attempt is made to perform the operative task, but is not completed due to weakness, pain or other obstruction. Only the first attempt is scored and the questions should be asked only once.

2. Gaze
The purpose of this item is to observe and score horizontal eye movements. To this end, use voluntary or reflexive stimuli and record a score of 1 if there is an abnormal finding in one or both eyes. A score of 2 is reserved for forced eye deviation that cannot be overcome by the oeulocephaIic maneuver. Do not do caloric testing. In aphasic or confused patients it is helpful to establish eye contact and prove about the bed. This item is an exception to the rules of using the first observable response and not coaching. 1n the patient who fails voluntary gaze, the oculocephalic maneuver, eye fixation, and tracking with the examiner's face, are used to provide stronger testing stimuli.

3. Visual Fields
Visual fields are tested exactly as demonstrated in the training video. Use finger counting or movement to confrontation and evaluate upper and lower quadrants separately. A score of 3 is reserved for blindness from any cause, including cortical blindness. A score of 2 is reserved for a complete hemianopia, and any partial visual field defect, including quadrant anopia, scores a 1.

4. Facial Movement (Facial Paresis)
Ask the patient "Show me your teeth ...now raise your eyebrows ...now close your eyes tightly". Assess the response to noxious stimulation in the aphasic or confused patient. A useful approach to scoring may be as follows: score a 2 for any clear cut upper motor neuron facial palsy. Normal function must be clearly demonstrated to obtain the score of 0. Anything in between, including flattened nasolabial fold, is scored a 1. The severely obtunded or comatose patient; patients with bilateral paresis, patients with unilateral lower motor neuron facial weakness would receive a score of 3.

5. Motor Arm-Right
Perform the test for weakness as illustrated in the video. When testing arms, palm must be down. Count out loud to the patient, until the limb actually hits the bed or other support. The score of 3 is reserved for the patient who exhibits no strength whatsoever, but does minimally move the limb on command when it is resting on the bed. The basic patient may understand what you are 'testing if you use the non-paretic limb first. Do not test both limbs simultaneously. Be watchful for an initial dip of the limb when released. Only score abnormal if there is a drift after the dip. Do not coach the patient verbally. Count out load in strong voice and indicate count using your fingers in full view of the patient. Begin counting the instant you release the limb. (Note that on some of the video illustrated patients, the examiners erroneously delay seconds before beginning to count).

6. Motor Arm-Left
See explanation of 5.

7. Motor Leg-Right
Perform the test for weakness as illustrated in the video. When testing motor leg the patient must be in the supine position to fully standardize the effect of gravity. Count out loud to the patient, until the limb actually hits the bed or other support. The score of 3 is reserved for the patient who exhibits no strength whatsoever, but does minimally move the limb on command when it is resting on the bed. The aphasic patient may understand what you are testing if you use the non paretic limb first. Do not test both limbs simultaneously. Be watchful for an initial dip of the limb when released. Only score abnormal if there is a drift after the dip. Do not coach the patient verbally. Count out load in strong voice and indicate count using your fingers in full view of the patient. Begin counting the instant you release the limb. (Note that on some of the video illustrated patients, the examiners erroneously delay seconds before beginning to count).

8. Motor Leg-Left
See explanation of 7.

9. Limb ataxia
Ataxia must be clearly present out of proportion to any weakness. Using the fingernose-finger and the heel-test, count the number of ataxic limbs, up to a maximum of two. The aphasic patient will often perform the test normally if first the limb is passively moved by the examiner. Otherwise the item is scored 0 for absent ataxia. If the weak patient suffers mild ataxia, and you cannot be certain that it is out of proportion to the weakness, give a score of 0. Remember this is scored positive only when ataxia is present. If the item is scored 00' or 09', skip to Item 12.

Please indicate presence of ataxia in arms and legs.

10. Sensory
Do not test limb extremities, i.e., hands and feet when testing sensation because an unrelated neuropathy may be present. Do not test through clothing.

11. Best Language
It is anticipated that most examiners will be ready to score this item based on information obtained during the history talang and the eight prior items. The attached picture and naming sheet therefore should be used to confirm your impression. It is common to find unexpected difficulties when the formal testing is done, and therefore every patient must be tested with the picture, naming sheet, and sentences. The score of 3 is reserved for the globally mute or comatose patient. NEW aphasia would score a 1. To choose between a score of l or 2 use all the provided materials; it is anticipated that a patient who missed more than two thirds of the naming objects and sentences or who followed only very few and simple one step commands would score a two. This item is an exception to the rule that the first response is used, since several different tools are used to assess language.

12. Dysarthria
Use the attached word list in all patients and do not tell the patient that you are testing clarity of speech. It is common to find slurring of one or more words in patients one might otherwise score as normal. The score of 0 is reserved for patients who read all words without any slurring. Aphasic patients and patients who do not read may be scored based on listening to the speech that they do produce or by asking them to repeat the words after you read them out loud. The score of 2 is reserved for the patient who cannot be understood in any meaningful way, or who is mute. On this question, normal speech must be identified to score a 0, so the unresponsive patient receives the score of 2.

13. Extinction and Inattention (formerly Neglect)
Place the hand in position exactly as shown in the training video. Fingers may be spread or together, The score of 0 is given only if the fingers maintain full extension of five seconds. The score of 2 is reserved for the hand that has no strength at all. Any change from the fully extended posture within five seconds scores a 1. Note: This item is open to significant variation among examiners, and all neurologists have slightly different methods of assessing neglect. Therefore, to the extent possible, test only double simultaneous stimulation to visual and tactile stimuli and score 2 if one side extinguishes to both modalities, a 1 if only to one modality. If the patient does not extinguish, but does show other well developed evidence of neglect, score a 1.
Total Score: Please provide the total score for the subject as determined by the 11 categories of questions. Do not include scores of "9" in total.

Appendix IV: Barthel Index

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

Patient Name: _____ **Rater:** _____ **Date:** __/__/__ ___ _____ __

Activity	Score
Feeding 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
Bathing 0 = dependent 5 = independent (or in shower)	_____
Grooming 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
Dressing 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
Bowels 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
Bladder 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident	_____

10 = continent	
Toilet Use 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
Transfers (bed to chair and back) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
Mobility (on level surfaces) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
Stairs 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0 - 100)	_____

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Appendix V: SF-12v2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
b	Climbing <u>several</u> flights of stairs	☐1	☐2	☐3

3. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
b Were limited in the <u>kind</u> of work or other activities	☐1	☐2	☐3	☐4	☐5

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a <u>Accomplished less</u> than you would like	☐1	☐2	☐3	☐4	☐5
b Did work or other activities <u>less carefully than usual</u>	☐1	☐2	☐3	☐4	☐5

5. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

6. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
b Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
c Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5

7. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

Appendix VI: Geriatric Depression Scale

Geriatric Depression Scale (Long Form)

Patient's Name:_____ Date:_____

Instructions: Choose the best answer for how you felt over the past week.

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	YES / NO	
2.	Have you dropped many of your activities and interests?	YES / NO	
3.	Do you feel that your life is empty?	YES / NO	
4.	Do you often get bored?	YES / NO	
5.	Are you hopeful about the future?	YES / NO	
6.	Are you bothered by thoughts you can t get out of your head?	YES / NO	
7.	Are you in good spirits most of the time?	YES / NO	
8.	Are you afraid that something bad is going to happen to you?	YES / NO	
9.	Do you feel happy most of the time?	YES / NO	
10.	Do you often feel helpless?	YES / NO	
11.	Do you often get restless and fidgety?	YES / NO	
12.	Do you prefer to stay at home, rather than going out and doing new things?	YES / NO	
13.	Do you frequently worry about the future?	YES / NO	
14.	Do you feel you have more problems with memory than most?	YES / NO	
15.	Do you think it is wonderful to be alive now?	YES / NO	
16.	Do you often feel downhearted and blue?	YES / NO	
17.	Do you feel pretty worthless the way you are now?	YES / NO	
18.	Do you worry a lot about the past?	YES / NO	
19.	Do you find life very exciting?	YES / NO	
20.	Is it hard for you to get started on new projects?	YES / NO	
21.	Do you feel full of energy?	YES / NO	
22.	Do you feel that your situation is hopeless?	YES / NO	
23.	Do you think that most people are better off than you are?	YES / NO	
24.	Do you frequently get upset over little things?	YES / NO	
25.	Do you frequently feel like crying?	YES / NO	
26.	Do you have trouble concentrating?	YES / NO	
27.	Do you enjoy getting up in the morning?	YES / NO	
28.	Do you prefer to avoid social gatherings?	YES / NO	
29.	Is it easy for you to make decisions?	YES / NO	
30.	Is your mind as clear as it used to be?	YES / NO	
		TOTAL	

This is the original scoring for the scale: One point for each of these answers.
Cutoff: normal-0-9; mild depressives-10-19; severe depressives-20-30.

1. NO	6. YES	11. YES	16. YES	21. NO	26. YES
2. YES	7. NO	12. YES	17. YES	22. YES	27. NO
3. YES	8. YES	13. YES	18. YES	23. YES	28. YES
4. YES	9. NO	14. YES	19. NO	24. YES	29. NO
5. NO	10. YES	15. NO	20. YES	25. YES	30. NO

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