The REFLECT Trial

A Randomized Evaluation oF the TriGuard™ HDH Cerebral Embolic Protection Device and the TriGUARD™ 3 Cerebral Embolic Protection Device to Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation

Clinical Investigation Plan
Version 13.0
November 1, 2018
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O.k.
Controlled Document
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1.0 Document Control

1.1 Version History

Version	Description
1.0 April 7, 2014	Original version submitted to FDA
2.0 December 1, 2014	Revised based on FDA Study Design Considerations
3.0 May 11, 2015	Revised based on FDA Study Design Considerations
4.0 July 6, 2015	Revised based on FDA Study Design Considerations
5.0 December 14, 2015	Updated description of device packaging; clarification of device regulatory status; clarification of CT imaging acquisition; minor additions to OUS adverse event reporting procedures; minor administrative changes.
6.0 September 28, 2016	Addition of quality of life assessment and supplemental neurocognitive assessment; addition of CT core laboratory for evaluation of anatomic eligibility criteria; clarification of data to be captured from post-procedure echocardiography performed as part of the standard of care; minor changes to study eligibility criteria (exclusion timeframe of prior stroke or TIA, range of concomitant vascular disease that would preclude delivery sheath access); clarification of protocol requirements for study-specific training for neurologists performing assessments; minor administrative changes.
7.0 January 13, 2017	Primary efficacy endpoint revised to include more clinically meaningful threshold and evaluation time point for MoCA worsening; hypothesis-driven secondary safety endpoints revised to add CNS infarction and total volume of cerebral ischemic lesions and omit stroke/TIA; additional prespecified exploratory analyses of primary and secondary efficacy endpoints; added NeuroARC-defined neurological events and “General Safety” composite to secondary safety endpoints; As Treated population modified to include all subjects exposed to the risks of the investigational device or procedure; mITT analysis population removed; revised assessment window for post-procedure NIHSS, mRS, and neuropsychological assessments to match post-procedure DW-MRI window; added frailty assessment at baseline and 90 days; added assessment of NYHA functional capacity, height, and weight at screening/baseline; eliminated select unnecessary blood chemistry tests from post-procedure assessment; updated device description to reflect changes to compatible commercially-available introducer sheaths; eliminated blinding of DSMC members based on DSMC request; updated Study Contacts; updated listing of investigators and investigational sites; minor administrative changes.
8.0 March 1, 2017	Reverted previous change to blinding of DSMC members (made in Version 7.0) based on FDA recommendation with DSMC agreement. DSMC members will be blinded to treatment allocation per protocol.

	The DSMC reserves the right to request unblinding if deemed necessary to protect subject rights, welfare, or well-being.
9.0 May 19, 2017	Increased total sample size from up to 375 subjects (285 randomized, 90 roll-in) to up to 495 subjects (405 randomized, 90 roll-in). This prospective increase in the number of allowable randomized subjects is intended to prevent a delay in further enrollment if the interim analysis determines that additional subjects are required to ensure adequate study power. Anticipated study timelines revised; additional minor administrative changes.
10.0 June 20, 2017	Revised total sample size to 445 subjects (355 randomized, 90 roll-in) in response to FDA feedback. The revised number of allowable randomized subjects will be sufficient to prevent a delay in further enrollment if the interim analysis determines that additional subjects are required to ensure adequate study power.
11.0 December 6, 2017- DSMB submission January 22, 2018- FDA submission	Protocol amendments due to incorporation of a next iteration device and following FDA feedback and DSMB comments on current protocol version. Changes include: Trial design- Addition of Phase II of the trial, incorporating a redesigned device (TriGUARD *3*) into the intervention arm and maintaining blinded data from the previous REFLECT trial Total number of expected subjects was updated to 533 including control patients from phase I. Randomization will be stratified by implanted valve type (Medtronic vs. Edwards). No single valve type will be implanted in more than approximately 70% of randomized patients (phase II). Event rate assumptions and sample size calculations- updated to reflect current RCT data and inclusion of controls from Phase I. Primary endpoint was updated- a new Tier 3 was added- Freedom from any MRI lesions to incorporate a meaningful clinical endpoint into the current hierarchy. MoCA assessment was excluded from this protocol as current data show inconclusive evidence concerning the validity and utility of this endpoint. 90 days clinical visit was changed to a telephone call to assess death and stroke to reflect that the Cerebral Embolic Protection Device (CEPD) is a peri-procedural device and should demonstrate its efficacy early. Assessment up to 30 days post procedure will ensure a correct balance between significant clinical efficacy and diminishing noise from other events such as atrial fibrillation. Other updates including fewer exclusion criteria due to next iteration device design, Cardiac biomarkers measurements only when clinically indicated and updated antiplatelet treatment recommendations to reflect current standard of care.

12.0 July 20, 2018 Post FDA-submission response	Protocol amendments following FDA feedback including: Event rate assumptions and sample size calculations- while event rates remained unchanged from the previous version, clarifications were added in regard to MRI findings and the comparison of lesion sizes between patients and to the FS methodology. Primary endpoints analysis detailed and clarified. Secondary sensitivity analyses added. Adaptive design added. Revised Statistical Code. Power calculations were updated following a revised statistical code Study Contacts updated Minor grammatical and format modifications
13.0 November 1, 2018 Post FDA Feedback on Version 12.0	Protocol amendments following FDA feedback, including: In Phase II, the primary efficacy endpoint and hypothesis-driven secondary endpoint comparisons will be one-sided with the level of significance set at 0.025. Text was corrected to reflect a one-sided analysis. Further clarifications to the adaptive design plan per FDA request. Revised total Phase II sample size to 345 subjects (295 randomized, 40-50 roll-in), from 275 subjects (225 randomized, 40-50 roll-in). The revised number of allowable randomized subjects will be sufficient to prevent a delay in further enrollment if the interim analysis determines that additional subjects are required to ensure adequate study power.

1.2 Protocol Approval Page

Study title: The REFLECT Trial

A randomized evaluation of the TriGuard™ HDH Cerebral Embolic Protection Device and the TriGUARD™ 3 Cerebral Embolic Protection Device to reduce the impact of cerebral embolic lesions after transcatheter aortic valve implantation

Protocol version: 13.0

Protocol date: November 1, 2018

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President and Chief Executive Officer
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VP Regulatory and Quality Affairs
Keystone Heart Ltd. — Date

1.3 Investigator Signature Page

Study title: The REFLECT Trial

A randomized evaluation of the TriGuard™ HDH Cerebral Embolic Protection Device and the TriGUARD™ *3* Cerebral Embolic Protection Device to reduce the impact of cerebral embolic lesions after transcatheter aortic valve implantation

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Investigator's Responsibility

Prior to participation in the REFLECT Trial, as the site principal investigator, I understand that I must obtain written approval from my Institutional Review Board/Ethics Committee. This approval must include my name and a copy must be provided to Keystone Heart Ltd. (or designee), along with the approved Patient Information and Consent Form prior to the first enrollment at my study site.

As the site Principal Investigator, I must also:

1. Conduct the study in accordance with the study protocol, the signed Clinical Investigation Agreement, applicable laws, 21 CFR Part 812 and other applicable United States Food and Drug Administration (FDA) regulations, any conditions of approval imposed by the FDA or IRB/EC, local regulations where applicable, International Conference on Harmonization (ICH) Good Clinical Practice guidelines, and the Declaration of Helsinki, and ensure that all study personnel are appropriately trained prior to any study activities.
2. Ensure that the study is not commenced until all approvals have been obtained.
3. Supervise all use of the TriGuard HDH Cerebral Embolic Protection Device and TriGUARD *3* Cerebral Embolic Protection Device at my institution.
4. Ensure that written informed consent is obtained from each subject prior to any data collection, using the most recent Institutional Review Board/Ethics Committee approved Patient Information and Consent Form.
5. Provide all required data and reports and agree to source document verification of study data with patient's medical records by Keystone Heart Ltd. (or designee) and any regulatory authorities.
6. Allow Keystone Heart Ltd. personnel or its designees, as well as regulatory representatives, to inspect and copy any documents pertaining to this clinical investigation according to national data protection laws.

Investigator Signature

I have read and understand the contents of the REFLECT Trial protocol and agree to abide by the requirements set forth in this document.

_____	_____
Investigator Name (print)	Investigative Site (print)
_____	_____
Investigator Signature	Date

2.0 Protocol Synopsis

Title:	The REFLECT Trial A Randomized Evaluation oF the TriGuard™ HDH Cerebral Embolic Protection Device and the TriGUARD™ *3* Cerebral Embolic Protection Device to reduce the impact of cerebral embolic LEsions after transCatheter aortic valve implanTation
Study device:	The Keystone Heart TriGuard™ HDH Cerebral Embolic Protection Device (CEPD) and TriGUARD™ *3* CEPD systems are aortic embolism protection devices intended to reduce the amount of embolic material that may enter the carotid, subclavian, and vertebral arteries during transcatheter heart valve implantation. **TriGuard HDH** The TriGuard HDH consists of a temporary, sterile, single use, biocompatible filter, introduced transfemorally through a 9F sheath to the aortic arch. Under fluoroscopic guidance, the device is positioned in the aortic arch to cover all 3 major cerebral arteries (innominate, left carotid, and subclavian arteries), and is held in position by an atraumatic stabilizer in the innominate artery. Once the device is in position, emboli and particulate matter are diverted away from the cerebral circulation and downstream to the descending aorta, where they are either harmless or can be treated effectively. The TriGuard HDH has received CE Mark and was commercially available in Europe and Israel during phase I. Use of the device at European and Israeli sites in the REFLECT study was in accordance with its market approved use. In the United States, the TriGuard HDH was for investigational use only. The device has received IDE approval for use in the REFLECT study (Phase I). **TriGUARD *3*** The TriGUARD *3* consists of a temporary, retrievable, sterile, single use, biocompatible filter, introduced transfemorally through an 8F sheath to the aortic arch. The TriGUARD *3* CEPD filter includes a self-stabilizing frame design, a reduced pore size filter mesh, and a redesigned delivery system intended for improved ease of use. Under fluoroscopic guidance, the device is positioned in the aortic arch to cover all major cerebral arteries (covering the innominate, left carotid, and left subclavian arteries), and is held in position by the device's circumferential pressure and the support of the nitinol shaft (external communicating device) in the aortic arch without the need for a stabilizer in the inominate artery. Once the device is in position, emboli and particulate matter are diverted away from the cerebral circulation and downstream to the descending aorta, where they are either harmless or can be treated effectively. The TriGUARD *3* device is for investigational use only.
Objective:	To assess the safety and efficacy of the TriGuard HDH and TriGUARD *3* cerebral embolic protection devices in patients undergoing transcatheter

	aortic valve implantation/replacement (TAVI[1]), in comparison with a control group of patients undergoing unprotected TAVI.
Study design[2]:	This prospective, single-blind, three arm, randomized, (2 device: 1 control), multicenter safety and efficacy trial is designed to enroll up to 603 total subjects in two consecutive phases: Phase I enrolled 258 subjects (including 54 Roll-Ins) and utilized the TriGuard HDH and Phase II will enroll up to 345 subjects (including 40-50 Roll-Ins) and will utilize the TriGUARD *3* (Figure 3b shows the patient flow/disposition). **Phase I** In phase I, a total of 204 evaluable subjects and 54 roll-in subjects were enrolled at 26 total investigational sites in the United States, Europe, and Israel, of which 20 sites were in the United States. A minimum of 50% of subjects were planned to be enrolled at US sites, and no single site was permitted to enroll more than 20% of all subjects. Subjects with indications for TAVI and who met study eligibility criteria were randomized 2:1 (stratified by study site) to one of two treatment arms: • **Intervention (Phase 1 Cohort)** – TAVI with the TriGuard HDH CEPD • **Control** – standard unprotected TAVI At sites where the investigator did not have prior experience with the TriGuard device (minimum of 2 prior cases), up to 3 roll-in subjects were enrolled. Roll-in subjects were not randomized, but underwent TAVI with the TriGuard HDH device. These cases were proctored by a Sponsor representative. Investigational sites with ≥2 prior TriGuard cases were allowed to enroll 1 roll-in subject at the discretion of the site principal investigator. All subjects were to be followed clinically in-hospital and at 30 and 90 days, and to undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and neurologic and neuropsychological testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 and 90 days. The initial randomized cohort expected to enroll up to 285 subjects. Note: Enrollment in Phase I has been halted after enrolling a total of 258 subjects (54 roll-ins and 204 randomized subjects including 63 controls) based on the recommendation of the Data Monitoring Committee following a review of interim 30-day data on 90 subjects at the prespecified interim analysis time point. A next iteration device designed for increased efficacy, ease of use, and improved safety will be tested in Phase II (below).

[1] Throughout the protocol, the term TAVI will be used to signify TAVI in OUS and TAVR in US.

[2] REFLECT Version 10.0 intended to enroll up to 355 subjects and up to 90 roll-ins. Enrollment in this cohort (termed Phase I in this protocol version) was halted based on the recommmendation of the independent DSMB following interim data review at the prespecified interim analysis timepoint, as well as availability of the redesigned TriGuard *3* system, after 204 subjects were randomized and 54 roll-ins were enrolled.

	Phase II In Phase II, up to 295 randomized subjects and 40-50 roll-in subjects will be enrolled at up to 25 sites in the United States (inclusive of sites enrolling subjects in Phase I). No single site will be permitted to enroll more than 20% of all randomized subjects in Phase II. Subjects with indications for TAVI and who meet study eligibility criteria will be randomized 2:1 (stratified by study site) to one of two treatment arms: • **Intervention** – TAVI with the TriGUARD *3* CEPD • **Control** – standard unprotected TAVI**.** Randomization will be stratified by implanted valve type (Medtronic vs. Edwards). No single valve type will be implanted in more than approximately 70% of randomized patients (phase II). Roll-in subjects (a minimum of 2 and a maximum of 3 Roll-ins per-site) will not be randomized, but will undergo TAVI with the TriGUARD *3* device. These cases will be proctored by a Sponsor representative. All subjects will be followed clinically in-hospital and at 30 days, undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and undergo neurologic (NIHSS) testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 days. A follow-up phone-call to assess the occurrence of death or stroke will be done at 90 days. The initial randomized cohort will consist of up to 225 subjects. After at least 50% of the initial randomized cohort (approximately 112 subjects) have reached the 30 day primary efficacy endpoint evaluation time point, a sample size reestimation will be performed in case the conditional power of the trial (assessed by the independent biostatistician) is >40% but <80%, subject to approval by the Sponsor. If this analysis determines that more than 225 randomized subjects will be required to ensure adequate study power, enrollment may continue until the required number of subjects have been enrolled, or until the total subject limit for the study has been reached (whichever occurs first).
Primary safety endpoint:	**Combined safety endpoint** (modified VARC 2 defined[1]) at 30 days, defined as a composite of death, stroke, life-threatening or disabling bleeding, acute kidney injury (stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure.
Primary efficacy endpoint: **(Phase II):**	**Hierarchical composite efficacy endpoint**, determined by pair-wise comparisons among all subjects according to the following pre-specified hierarchy of adverse outcomes: • All-cause mortality and/or any stroke (fatal and non-fatal, disabling or non-disabling) [evaluated at 30 days] o If both had a death/stroke a time to event analysis by days will determine a win

	○ If both patients had a stroke at the same day the comparison moves to the next tier • NIHSS worsening (increase from baseline) [evaluated at 2 to 5 days post-procedure] • Freedom from any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure • Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure Each subject in the intervention group will be compared with each and every subject from the control group based on the above hierarchy according to the Finkelstein-Schoenfeld method.[2] For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke, the patient with the later event will be the winner. If both have death/stroke on same day it is equilibrium (score 0). If both subjects are alive and have a stroke on the same day, the comparison moves to the next tier of the hierarchy (NIHSS worsening). If both subjects survive free of stroke to 30 days, the comparison also moves to the next tier of the hierarchy. After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared.
Secondary endpoints:	**SECONDARY SAFETY ENDPOINTS** The following safety endpoints will be evaluated in-hospital and at 30 days. Overall event rates will be reported by treatment group. In the Intervention and Roll-In groups, all safety endpoints will be adjudicated for their relationship to the investigational device and/or the investigational procedure by an independent Clinical Events Committee. **In-hospital procedural safety,** defined as the composite of the following Major Adverse Cardiovascular and Cerebrovascular Events (MACCE): • All-cause mortality • All stroke (disabling and non-disabling) • Life-threatening (or disabling) bleeding • Acute kidney injury – Stage 2 or 3 (including renal replacement therapy) • Major vascular complications **TAVI device success** (VARC), evaluated in-hospital, defined as: • Absence of procedural mortality AND • Correct positioning of a single prosthetic heart valve into the proper anatomical location AND

	• Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (VARC-defined) and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation (VARC-defined) (site-reported) **General Safety**, defined as the composite of the following adverse events: • All-cause mortality • All stroke (disabling and non-disabling) • Acute kidney injury – Stage 3 (including renal replacement therapy) **Mortality: [evaluated in-hospital and at 30 and 90 days]** • All-cause mortality o Cardiovascular mortality ▪ Neurologic event related mortality o Non-cardiovascular mortality **Myocardial infarction:** • Peri-procedural MI (≤72 hours after the index procedure) • Spontaneous MI (>72 hours after the index procedure) **Neurological Events** (component and composite): • Stroke (VARC-2 defined) **[evaluated in-hospital and at 30 and 90 days]** o Ischemic stroke o Hemorrhagic stroke o Undetermined • Disabling Stroke (VARC-2 defined) **[evaluated in-hospital and at 30 and 90 days]** • Non-disabling stroke (VARC-2 defined) **[evaluated in-hospital and at 30 and 90 days]** • Transient ischemic attack (TIA) (VARC-2 defined) • Overt CNS Injury (NeuroARC[3] defined Type 1) **[evaluated in-hospital and at 30 and 90 days]** • Covert CNS Injury (NeuroARC defined Type 2) • Neurological dysfunction without CNS injury (NeuroARC defined Type 3) • CNS infarction (NeuroARC defined composite neurological endpoint) • CNS hemorrhage (NeuroARC defined composite neurological endpoint) **Bleeding Complications:**

- Life-threatening bleeding (VARC-2)
- Major bleeding
- Minor bleeding

Acute Kidney Injury (AKIN Classification):

- Stage 2
- Stage 3

Vascular Complications:

- Major vascular complications
- Major vascular complications related to TriGUARD *3*

SECONDARY EFFICACY ENDPOINTS

Hypothesis-driven Secondary Endpoints (Phase II)

For the following secondary endpoints, a test for superiority of each intervention group to the control group will be performed. To address the issue of multiple tests among these secondary endpoints, sequential testing is planned. Secondary endpoints will be formally tested if and only if the primary study hypotheses are confirmed. The secondary endpoints will be tested individually, in the order in which they are listed as follows:

- **All stroke** [evaluated at 7 days in the eITT population]
- **NIHSS worsening**, defined as any NIHSS score increase from baseline [evaluated at 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]. A sensitivity analysis will further compare $\geq$2 points NIHSS worsening [evaluated at 2-5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]
- **Composite of all-cause mortality and all stroke** [evaluated at 7 days in the eITT population]
- **CNS Infarction** (NeuroARC defined) [evaluated at 30 days in the eITT analysis population]
- **Total volume of cerebral ischemic lesions** detected by DW-MRI, [evaluated 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

The above endpoints will be tested by this pre-specified sequence, until the first non-significant difference is found between the two treatment groups. After that, other treatment comparisons will be examined in an exploratory manner.

Phase I: Hierarchical composite efficacy endpoint, determined by pair-wise comparisons among all subjects according to the following pre-specified hierarchy of adverse outcomes:

- All-cause mortality or any stroke (disabling or non-disabling) [evaluated at 30 days]

- NIHSS worsening (increase from baseline) [evaluated at 2-5 days post-procedure] or Montreal Cognitive Assessment worsening (decrease of 3 or more points from baseline) [evaluated at 30 days]
- Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure

Each subject in the intervention group will be compared with each and every subject from the control group based on the above hierarchy according to the Finkelstein-Schoenfeld method.[2] For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke, it is equilibrium (score 0). If both subjects survive free of stroke to 30 days, the comparison moves to the next tier of the hierarchy.

After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared.

Imaging Efficacy Endpoints (Phase I and II)

- **Presence of cerebral ischemic lesions** detected by DW-MRI, evaluated 2 to 5 days post-procedure
- **Number of cerebral ischemic lesions** detected by DW-MRI, evaluated 2 to 5 days post-procedure
- **Per-patient average single cerebral ischemic lesion volume** detected by DW-MRI, evaluated 2 to 5 days post-procedure
- **Single cerebral ischemic lesion volume** (lesion-level analysis) detected by DW-MRI, evaluated 2 to 5 days post-procedure
- **Total volume of cerebral ischemic lesions** detected by DW-MRI, evaluated 2 to 5 days post-procedure

Neurologic Efficacy Endpoints (Phase I and II)

- **NIHSS worsening**, defined as an NIHSS score increase from baseline [baseline score compared with score evaluated at 2-5 days post-procedure and at 30 days]
- **New neurologic impairment**, defined as NIHSS worsening from baseline accompanied by the presence of cerebral ischemic lesions [evaluated at 2-5 days post-procedure and at 30 days]

SECONDARY PERFORMANCE ENDPOINTS

The following performance endpoints will be evaluated post-procedure in the Intervention group (Roll-Ins excluded) (TriGuard HDH and TriGUARD *3* reported individually):

- **Successful device deployment,** defined as ability to access the aortic arch with the TriGuard HDH or TriGUARD *3* delivery catheter and deploy the device from the delivery catheter into the aortic arch

	• **Device positioning,** defined as ability to position the TriGuard HDH or TriGUARD *3* device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by fluoroscopy) until the following time points: o Final deployment of the first prosthetic valve o Final procedure (after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed) Extent of cerebral artery coverage will be reported as: o Complete (coverage of all 3 cerebral artery branches) o Partial (coverage of 1-2 cerebral artery branches) o None *Note:* Maintenance of device positioning to each time point and extent of cerebral artery coverage will be evaluated by the Angiographic Core Laboratory. • **Device interference**, defined as interaction of the TriGuard HDH or TriGUARD *3* device with the TAVI system leading to: o Inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR o Inability to deploy the TAVI valve prosthesis, OR o Inability to retrieve the valve prosthesis or delivery system • **Successful device retrieval**, defined as ability to retrieve the TriGuard HDH or TriGUARD *3* CEPD. • **Technical success,** defined as successful device deployment, device positioning, and successful device retrieval in the absence of device interference • **Procedure success**, defined as technical success in the absence of any investigational device-related or investigational procedure-related in-hospital procedural safety events
Other measures:	The following additional measures will also be reported (TriGuard HDH and TriGUARD *3* reported individually): o **Device deployment time** − Time elapsed between insertion of the TriGuard HDH or TriGUARD *3* device into the groin access point and successful device deployment [evaluated post-procedure] o **Total procedural time** − Time elapsed between first arterial access and removal of the last catheter from the arterial access sheath [evaluated post-procedure] o **Total fluoroscopy time** [evaluated post-procedure] o **Total contrast utilization** [evaluated post-procedure]

	○ **Health-related quality of life, as measured by the SF-36 Health Survey** [evaluated at baseline and at 30 days, Phase I only].
Patient population:	The study will enroll up to 603 subjects (499 randomized subjects and up to 104 roll-in subjects) meeting approved indications for transcatheter aortic valve implantation. Of these, up to 295 will be randomized in Phase II, with an additional 40-50 roll in patients.
Patient Follow-Up:	Phase I: All subjects were followed clinically in-hospital and at 30 and 90 days, underwent diffusion-weighted MR imaging 2 to 5 days post-procedure, and underwent neurologic and neuropsychological testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 and 90 days. Phase II: All subjects will be followed clinically in-hospital and at 30 days, undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and undergo neurologic testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 days. 90 days phone-call follow-up will assess the occurrence of death and/or stroke.
Study Committees:	**Patient Review Committee** A Patient Review Committee (PRC) will evaluate each potentially eligible subject (Includes confirmation that subject meets selected anatomic eligibility criteria based on imaging analysis by an independent CT core laboratory). All subjects must be approved by the PRC prior to enrollment in the trial. **Clinical Events Committee** An independent Clinical Events Committee (CEC) will adjudicate all site-reported cardiovascular adverse events and all site-reported adverse events potentially meeting endpoint criteria, in an ongoing fashion during the trial. In the Intervention and Roll-In groups, relationship to the investigational device or investigational procedure will also be adjudicated. **Data and Safety Monitoring Board** An independent Data and Safety Monitoring Board (DSMB) will be responsible for the oversight and safety monitoring of the study. The DSMB will advise the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.
Antiplatelet Therapy:	Selection and dosing of antiplatelet therapy will be performed according to physician standard practice, in accordance with local standards of care and published guidelines for TAVI procedures. Each site is encouraged to commit to a consistent antiplatelet regimen to be applied to all subjects enrolled in the trial, independent of treatment group. The investigators recommend (but do not require) the following antiplatelet regimen, and further recommend that all subjects receive dual anti-platelet therapy for a minimum of 6 months in the absence of contraindications: • ASA 75-100 mg maintenance dose indefinitely, and • Clopidogrel 75 mg daily maintenance dose

	• If the patient is on warfarin therapy prior to the procedure the following is recommended: o Discontinue warfarin three days prior to the procedure o Confirm that the INR is <1.8 prior to the procedure o Clopidogrel 75 mg for 3 days or ASA 75-100 mg prior to the procedure • If the patient is on warfarin therapy post-procedure it is recommended that the patient is prescribed either daily aspirin (75-100 mg) or daily clopidogrel (75 mg) Minimum recommended maintenance dosages can be higher based on physician's discretion.
Inclusion criteria:	Subjects must meet **ALL** of the following criteria: ***General Inclusion Criteria*** 1. The patient is a male or non-pregnant female ≥18 years of age 2. The patient meets indications for TAVI 3. The patient is willing to comply with protocol-specified follow-up evaluations 4. The patient, or legally authorized representative, has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC).
Exclusion criteria:	Potential subjects will be excluded if **ANY** of the following criteria apply: ***General Exclusion Criteria*** 1. Patients undergoing TAVI via the trans-apical, trans-axillary, trans-subclavian, or trans-aortic route (applicable to Phase II) 2. Patients undergoing TAVI via the trans-apical approach due to friable or mobile atherosclerotic plaque in the aortic arch (*Phase I only*) 3. Patients with a previously implanted prosthetic aortic valve (i.e., planned valve-in-valve TAVI) 4. Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 14 days prior to index procedure per site standard test 5. Patients with known diagnosis of acute myocardial infarction (AMI) within 72 hours preceding the index procedure (according to definition) or AMI >72 hours preceding the index procedure, in whom CK and CK-MB have not returned to within normal limits at the time of procedure, or patients who are currently experiencing clinical symptoms consistent with new-onset AMI, such as nitrate-unresponsive prolonged chest pain 6. Patients with a history of bleeding diathesis or coagulopathy or patients in whom anti-platelet and/or anticoagulant therapy is contraindicated,

	patients who will refuse transfusion, or patients with an active peptic ulcer or history of upper gastrointestinal (GI) bleeding within the prior 3 months 7. Patients with known mental or physical illness or known history of substance abuse that may cause non-compliance with the protocol, confound the data interpretation, or is associated with a life expectancy of less than one year 8. Patients with severe allergy or known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, clopidogrel, nitinol, stainless steel alloy, and/or contrast sensitivity that cannot be adequately pre-medicated 9. Patients with a history of a stroke or transient ischemic attack (TIA) within the prior 6 months 10. Patients with renal failure (estimated Glomerular Filtration Rate [eGFR] <30 mL/min calculated from serum creatinine by the Cockcroft-Gault formula or MDRD- Modification of Diet in Renal Disease formula) 11. Patients with hepatic failure (Child-Pugh class C) 12. Patients with hypercoagulable states that cannot be corrected by additional peri-procedural heparin 13. Patients presenting with cardiogenic shock at the time of the index procedure 14. Patients with severe peripheral arterial, abdominal aortic, or thoracic aortic disease that precludes delivery sheath vascular access 15. Patients in whom the aortic arch (*Phase I and II*), innominate artery ostium *(Phase I only)*, or proximal innominate artery (*Phase I only*) are heavily calcified, severely atheromatous, or severely tortuous 16. Patients with an innominate artery ostium diameter <10 mm or >25 mm (*Phase I only*) 17. Patients with a transverse aortic diameter >43 mm (*Phase I only*) 18. Patients with anatomic irregularities of the innominate artery that could prevent positioning of the TriGuard upper stabilizer and compromise stability of the device (*Phase I only*) 19. Patients with any other condition that would prevent adherence to the TriGuard HDH (Phase I) or TriGUARD *3* (Phase II) Instructions for Use 20. Patients with contraindication to cerebral MRI 21. Patients who have a planned treatment with any other investigational device or procedure during the study period 22. Patients planned to undergo any other cardiac surgical or interventional procedure (e.g., concurrent coronary revascularization) during the TAVI procedure or within 10 days prior to the TAVI procedure. NOTE: Diagnostic cardiac catheterization <u>is</u> permitted within 10 days prior to the TAVI procedure.

Blinding	This is a single-blind study. The following individuals will be blinded to the subject's treatment allocation: • Subject and his/her family members • Site personnel administering neurological evaluations (NIHSS or mRS and/or neuropsychological test battery in Phase I); these individuals will also be blinded to DW-MRI results • Members of the Data and Safety Monitoring Board • MRI Core Laboratory personnel performing imaging analysis Un-blinding will occur only after the database has been locked for the analysis of the primary endpoint or to protect subject rights, welfare, or well-being at the request of the DSMB.
Analysis Plan:	***Primary Endpoint Analysis*** **Primary Safety Endpoint Analysis** **(Phase I and II[3] reported individually)** The primary safety hypothesis is that the rate of the VARC 2 Combined Safety Endpoint (defined as the composite of death, stroke, life-threatening or disabling bleeding, AKI [Stage 2/3], coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure) at 30 days in the group undergoing TAVI with either protection device system (Intervention groups) is significantly less in each device group (TriGuard HDH and TriGUARD *3*) compared separately to the Performance Goal (PG). The PG has been determined based on published literature reporting the VARC-2 combined safety endpoint in patients undergoing TAVI with Medtronic or Edwards Valves. Based on an expected event rate of 25% and a relative non-inferiority delta of 37.5% (absolute delta 9.4%), the PG will be set at 34.4% (25% + 9.4%). A sample size of 179 evaluable subjects in the intervention group will provide 85% power to demonstrate that the intervention group event rate is significantly less than the PG at the alpha=0.05 level. After accounting for a potential 5% loss to clinical follow-up at 30 days (including subjects who do not meet As Treated population criteria), the total required intervention group sample size is 190 subjects in each Phase. For Phase II, the 150 subjects randomized to the TriGUARD *3* and 40-50 roll-ins will constitute the primary safety population. The primary analysis population for the primary safety endpoint will be the As Treated (AT) population. The AT population is defined by the treatment actually received, regardless of the assigned treatment. In the AT population, subjects in whom vascular access in the contralateral femoral artery has been established for the intended deployment of the TriGuard HDH or TriGUARD *3* device will be assigned to the Intervention group, and subjects

[3] Safety power calculation was done for TriGUARD *3* independently.

in whom the TAVI procedure is initiated (but no vascular access for intended deployment of the TriGuard HDH or TriGUARD *3* is established) will be assigned to the Control group. As a secondary analysis, the primary safety endpoint will be evaluated in the Intention To Treat (ITT) population of evaluable subjects (Roll-In patients are excluded).

Primary Efficacy Endpoint Analysis

Phase II:

The primary efficacy hypothesis is that TAVI with the TriGUARD *3* system is superior to standard (unprotected) TAVI for the primary hierarchical composite efficacy endpoint of all-cause mortality or any stroke at 30 days (Tier 1), NIHSS worsening 2-5 days post-procedure (Tier 2), freedom from any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure (Tier 3), and total volume of post-procedure cerebral ischemic lesions detected by DW-MRI (Tier 4). In tier 1 death/stroke will be analyzed as time to event by days.

Each subject in the intervention group of phase II will be compared with every control subject (from phases I and II) based on the pre-specified hierarchy of adverse outcomes according to the Finkelstein-Schoenfeld method.[2] For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke on the same day, it is equilibrium (score 0, otherwise the patient with the later (by at least a day) death/stroke will be the winner. If both patients had a stroke on the same day the comparison will move to the next tier of the hierarchy.

If neither subject experiences a Tier 1 event, the comparison moves to the next tier of the hierarchy. After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared by the chi-square test.

Based on published clinical data from randomized controlled trials of subjects undergoing TAVI[4-7] as well as data from the DEFLECT III randomized trial of TriGuard HDH vs. unprotected TAVI[8] and the recent SENTINEL[9] trial we assume the following hierarchical event rates:

Assumed Event Rates Phase II

	Assumed Control Rates	**Assumed TriGUARD *3* Rates**
Death or Stroke	11%	6%
Worsening NIHSS	9%	6%
Freedom from MRI Findings (Lesion Volume 0 mm³)	11%	27%
Lesion Volume (mm³)		
>0-50	7%	19%
>50-150	33%	7.5%
> 150	48%	46%

15% Missing in MRI Follow-up and 5% missing for all other parameters
Type I Error = 5%

Among subjects who reach third tier of the comparison hierarchy, we assume a 15% loss to DW-MRI follow-up (due to contraindications to post-procedure DW-MRI [e.g., pacemaker implantation] or subject non-compliance).

Given these assumptions, the initial randomized cohort sample size of 225 subjects (2:1 randomization with 150 Intervention and 75 new control patients) will provide a power of >80% to demonstrate superiority (1-sided α=0.025) of the intervention group over the control group for the primary efficacy endpoint. Notably, in several simulations, considering different distributions for lesion volume and different distributions for death/ stroke, the study power remained greater than 80%. Adding the 63 control subjects already enrolled in REFLECT phase I for a total of 138 control subjects would increase the power to at least 92% to demonstrate superiority of the primary efficacy endpoint; poolability of the Phase I and Phase II control subjects will be assessed at the time of the primary analysis and the results will determine the control population used for the primary analysis of the primary efficacy endpoint. 5% loss to clinical follow up at 30 days is included.

As a primary efficacy analysis, the primary efficacy endpoint will be evaluated in the efficacy Intention to Treat (eITT) population. The eITT population is defined as:

- Subjects who are enrolled in the trial and randomized to a treatment group, regardless of treatment actually received AND
- Who do not have conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI

Selection of the eITT population as the primary analysis population for the primary efficacy endpoint ensures that, should a small number of subjects experience an adverse event due to circumstances unrelated to procedural neuroprotection (i.e., conversion to surgery or prolonged cardiac arrest prior to the post-procedure DW-MRI), the study will remain powered to detect a clinically-meaningful treatment effect, particularly regarding the volume of subclinical cerebral ischemic lesions on DW-MRI.

If the primary endpoint is met in the primary (eITT) analysis population, sequential testing of the primary efficacy hypothesis will be conducted in the Intention to Treat (ITT) analysis population of evaluable subjects (Roll-In patients are excluded). As a secondary analysis, the primary efficacy endpoint and its components will be evaluated in the Intention To Treat (ITT) analysis population of evaluable subjects (Roll-In patients are excluded). The ITT population is defined as all subjects who are enrolled the study, by assigned treatment, regardless of the treatment actually received. An additional analysis will also be performed in the Per Treatment (PT) Population.

The PT population is defined as subjects in the Intervention group in whom device positioning is maintained until final procedure with complete cerebral coverage, and all Control group subjects. An additional analysis of the

primary efficacy endpoint with adjustment for pre-existing cerebral lesion volume will also be performed in the primary eITT analysis population.

***Secondary Endpoints Analysis* (Phase I)**

The efficacy hypothesis for phase I was that TAVI with the TriGuard HDH system is superior to standard (unprotected) TAVI for the phase I hierarchical composite efficacy endpoint of all-cause mortality or any stroke at 30 days (Tier 1), NIHSS worsening 2-5 days post-procedure or MoCA worsening at 30 days (Tier 2), and total volume of post-procedure cerebral ischemic lesions detected by DW-MRI (Tier 3).

Each subject in the intervention group was to be compared with every subject from the control group based on the pre-specified hierarchy of adverse outcomes according to the Finkelstein-Schoenfeld method[2]. For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke, it is equilibrium (score 0). If neither subject experiences a Tier 1 event, the comparison moves to the next tier of the hierarchy. After all between-subject comparisons have been performed, scores were to be summed to obtain a cumulative score for each subject, then outcomes between treatment (TriGuard HDH and control) groups were to be compared by the Mann-Whitney test.

Based on published clinical data from randomized controlled trials of subjects undergoing TAVI as well as data from the DEFLECT III randomized trial of TriGuard vs. unprotected TAVI, we assumed the following hierarchical event rates:

Event	Intervention	Control
Death or stroke	7%	8%
NIHSS or MoCA worsening	10%	15%
Total Lesion Volume	70 mm^3	100 mm^3

In addition, among subjects who reach Tier 3 of the comparison hierarchy, we assume a 20% loss to DW-MRI follow-up (due to contraindications to post-procedure DW-MRI [e.g., pacemaker implantation] or subject non-compliance).

Given these assumptions, a sample size of 270 evaluable subjects (180 Intervention and 90 Control) would provide >90% power to demonstrate superiority (2-sided α=0.049) of the Intervention group to the Control group for the primary efficacy endpoint. Therefore, the total sample size of the initial randomized cohort of 285 subjects (190 Intervention and 95 Control) will provide sufficient power to evaluate the primary efficacy endpoint, even in the event that up to 5% of trial subjects do not meet criteria for inclusion in the primary efficacy analysis population**

*** Enrollment in this cohort (termed Phase I in this protocol version) was halted after 204 subjects were randomized and 54 roll-ins were enrolled).*

Secondary Safety Endpoints

All secondary safety endpoints will be reported by treatment group in the AT population of evaluable subjects using appropriate descriptive statistics (sample size, mean, standard deviation, median, minimum, and maximum for continuous characteristics; counts and percentages of patients for dichotomous characteristics). No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints.

The AT analysis will be considered primary. As a secondary analysis, all secondary safety endpoints will be evaluated in the ITT population of evaluable subjects.

For safety endpoints occurring in the Intervention and Roll-In groups, relationship to the investigational device/investigational procedure (as determined by an independent Clinical Events Committee) will also be reported.

Secondary Efficacy Endpoints

Imaging Efficacy Endpoints

All secondary imaging efficacy endpoints will be reported by treatment group in the eITT population of evaluable subjects (Roll-In subjects are excluded) with interpretable DW-MRI data using descriptive statistics.

No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints. Statistics for continuous variables will include mean, median, quartiles, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group.

The analysis of the eITT population of subjects with available DW-MRI data will be considered primary. As a secondary analysis, all secondary imaging efficacy endpoints will be evaluated in the ITT population of evaluable subjects. An additional analysis will also be performed in the PT population. An additional analysis of secondary imaging efficacy endpoints with adjustment for pre-existing cerebral lesion volume will also be performed in the primary eITT analysis population.

Neurologic Efficacy Endpoints

All secondary neurologic efficacy endpoints will be reported by treatment group in the eITT Population of evaluable subjects (Roll-In subjects are excluded) using descriptive statistics. No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints. Statistics for continuous variables will include mean, median, quartiles, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group

	The analysis of the eITT population will be considered primary. As a secondary analysis, all secondary neurologic and cognitive efficacy endpoints will be evaluated in the ITT population of evaluable subjects. An additional analysis will also be performed in the PT population. An additional analysis of secondary neurologic and cognitive efficacy endpoints with adjustment for pre-existing cerebral lesion volume will also be performed in the primary eITT analysis population. **Secondary Performance Endpoints** All secondary performance endpoints will be reported by treatment group in the ITT population of evaluable subjects (Roll-In subjects are excluded) using appropriate descriptive statistics (sample size, mean, standard deviation, median, minimum, maximum for continuous characteristics; counts and percentages of patients for dichotomous characteristics). No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints. The ITT analysis will be considered primary. As an additional analysis, all secondary performance endpoints will be evaluated in the AT population of evaluable subjects. **Other Measures** Other Measures will be reported by treatment group in the ITT population of evaluable subjects (Roll-In subjects are excluded) using descriptive statistics. No formal hypothesis testing will be performed. The ITT analysis will be considered primary. As a secondary analysis, Other Measures will be evaluated in the AT population of evaluable subjects. An additional analysis will also be performed in the PT population. **Subgroup Analyses** Subgroup analyses will be performed for all primary and secondary endpoints in their respective primary analysis populations for the following subgroups, and results will be reported by treatment group using descriptive statistics: • Subjects with paroxysmal or persistent atrial fibrillation (AF) at baseline • Subjects by valve prosthesis type (Edwards vs. Medtronic) **Roll-In Population Analysis** The Phase II Roll-In population will be pooled with the Phase II intervention group for the primary analysis of the primary safety endpoint. The Roll-In patient population will also be used for a separate analysis of all primary and secondary endpoints and other measures. Additional analyses will evaluate primary and secondary endpoints in the pooled population of Roll-In Subjects plus Evaluable Subjects. ***Analysis Timing and Adjustment*** **Interim Analysis (Phase I only)** The assumptions for powering the primary efficacy endpoint were based on neurologic, cognitive, and imaging data from a limited number of subjects in

	the DEFLECT III Trial. Due to uncertainty regarding the primary efficacy endpoint, an unblinded interim analysis was planned to be conducted to re-evaluate the sample size required to demonstrate superiority of the Intervention group to the Control group. The unblinded interim analysis was to be conducted when 90 subjects total (approximately 60 Intervention group subjects and 30 Control group subjects) who meet the eITT population definition have completed the 30-day follow-up visit. At the interim analysis, the trial sample size would have been re-calculated, if necessary, to ensure 80% conditional power to demonstrate superiority (overall 2-sided α=0.05) of the Intervention group to the control group for the primary efficacy endpoint, taking into account the interim unblinded results, according to the eITT population definition (there was to be no imputation of missing data in this interim analysis; i.e., missing data will be excluded). The conditional power and sample size re-calculation for the final analysis was planned to be ascertained by computer simulations and by established methodology outlined in Chen, DeMets and Lan.[10] Specifically, at the interim stage, Monte Carlo simulations were to be used to assess the conditional power of achieving a significant Mann-Whitney test by the end of the study, conditioned on the distribution of the observed interim data. If the conditional power was found to be 50% - 80% (the "promising zone" according to Chen, DeMets and Lan), the plan was to use simulations to ascertain the increase in sample size that is required to yield 80% conditional power for the Mann-Whitney test. If the interim analysis determined that more than 285 randomized subjects will be required to ensure adequate study power, enrollment would have continued until the required number of subjects have been enrolled, or until the total subject limit for the study has been reached (whichever occured first). If the conditional power was found to be <50% or >80%, the study would have proceeded as is without a sample size adjustment (i.e., only the initial randomized cohort of 285 subjects would have been enrolled). There was no intention to stop the study for overwhelming efficacy at the interim analysis. However, as a precautionary measure and to be conservative (due to the presence of an unblinded interim analysis), the O'Brien Fleming alpha spending method was to be used to calculate an alpha penalty for the final analysis regardless of whether a sample size increase is needed (final analysis two-sided alpha = 0.049). Note: Enrollment in Phase I (TriGuard HDH CEPD) has been halted after enrolling a total of 258 subjects (54 roll-ins and 204 randomized subjects including 63 controls) based on a recommendation of the DSMB following data review at the prespecified interm analysis time point. A next iteration device (TriGUARD *3*) designed for increased efficacy, ease of use, and improved safety will be tested in Phase II. **Adaptive Design (Phase II)** Once at least 50% of the Phase II cohort has been enrolled and has reached the 30 day primary efficacy endpoint evaluation time point, the independent unblinded statistician will perform a conditional power analysis. If the trial, based on the results at that point is either ≤ 40% powered to achieve success

	in meeting the primary endpoint or is ≥80% powered to achieve the primary endpoint, no sample size reestimation will be required. If the conditional power of the study is >40% but <80% the independent unblinded statistician will recommend a sample size reestimation, subject to approval by the Sponsor. *Promising zone computation* After the trial has enrolled 50% of the originally planned sample size of the initial randomized cohort (approximately 112 subjects), an independent statistician will estimate all 4 levels of the Finkelstein-Schoenfeld hierarchy for device and control, and use these estimates to re-calculate the trial's power given the originally planned 225 Phase II patients. If the trial power is between >40% and <80%, the trial will be considered promising and the trial will readjust the sample size to attain 80% power. If on the other hand the power falls to ≤ 40% or to ≥ 80%, the sample size will not be adjusted. *Conditional power computation* The conditional power will estimate all four Finkelstein-Schoenfeld levels and use these estimates to simulate future enrolled patients. The power simulation will follow exactly the same algorithm as used to power the original Phase II study with updated estimates of effect size. *Alpha spending and controlling type I error* Since the study leadership and sponsor do not conduct any formal statistical hypothesis test, this design will not incur any alpha penalty or affect the overall type I error. As detailed by Mehta and Pocock[11] and based on the work of Chen[10] as long as the sample size reestimation occurs only when the conditional power falls in the promising zone, no additional alpha spend is required and the overall type I error is preserved.	
Anticipated timelines:	**Phase I**	
	Initial Enrollment:	June 2016
	Last Enrollment:	July 2017
	30 days follow-up:	September 2017
	90 days follow-up:	November 2017
	Phase II	
	Initial Phase II Enrollment:	June 2018
	Last Enrollment:	December 2018
	30 days follow-up:	January 2019
	90 days follow-up:	March 2019

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4.0 Introduction

4.1 Background

4.1.1 **Periprocedural Stroke**

Stroke is a dreaded complication of endovascular procedures due to its association with an extreme morbidity and mortality burden.[12, 13] Periprocedural stroke rates increase with the complexity of cardiac surgery, ranging from 1-5% for coronary artery bypass graft surgery (CABG) or isolated aortic valve replacement to as high as 7.4% for combined CABG and valve surgery and 9.7% for multiple valve surgery.[14] Periprocedural stroke during catheter-based cardiovascular procedures is also a major concern. While stroke after left heart catheterization or percutaneous coronary intervention (PCI) is rare (<0.5%),[15] it is associated with significant morbidity and an in-hospital mortality rate of 25% to 30%.[16, 17]

Cerebral microembolism is the primary mechanism of periprocedural stroke during catheter-based interventions, and is primarily caused by embolization of aortic plaque dislodged during retrograde instrumentation of the aortic arch.[18] In particular, retrograde catheterization with crossing of the aortic valve has been associated with focal diffusion-imaging abnormalities suggesting cerebral embolic events in 22% of patients, in addition to a 3% rate of clinical neurological deficits.[19]

Given the frequency and dire implications of periprocedural stroke, methods to reduce cerebral embolism during cardiac interventions are sorely needed.

4.1.2 **Transcatheter Aortic Valve Implantation and Cerebral Injury**

4.1.2.1.1 TAVI and Periprocedural Stroke

Transcatheter aortic valve implantation (TAVI) has emerged as an important alternative to surgical aortic valve replacement (SAVR) for high-risk and moderate-risk patients with aortic stenosis, offering overall less morbidity, similar mortality and significantly reduced recovery time.[4, 20-22] However, periprocedural neurological injury remains an important limitation of TAVI. In high-risk surgical candidates in the randomized PARTNER trial, TAVI was associated with an approximately two-fold increased risk of stroke or TIA (5.5% vs. 2.4%, p=0.04) compared with SAVR at 30 days.[4] In inoperable subjects, stroke or TIA occurred in 6.7% of TAVI patients at 30 days, with 5.0% of subjects suffering a major stroke.[5] A meta-analysis of 10,037 published TAVI patients found an overall 30-day stroke rate of 3.3±1.8%, with the majority being major strokes (2.9±1.8%).[23] In this study, stroke was associated with a more than 3.5-fold increase in 30-day mortality (25.5±21.9% vs. 6.9±4.2%).

In the more recent PARTNER 2 trial, the rates of any stroke in moderate risk patients with AS after TAVI were similar to the rates after SAVR: 5.5% vs. 6.1% at 30 days and as high as 9.5% vs. 8.9% at 2 years, for TAVI and SAVR respectively.[22]

The timing of stroke after TAVI follows a bimodal distribution. The risk of stroke during an early high-peaking hazard phase (within 2 days of the procedure) is primarily procedure-related (TAVI versus SAVR).[24] More than 50% of strokes in TAVI patients occur during this early phase. During a later constant hazard phase (1 to 12 months post-procedure), patient factors including generalized heavy atherosclerotic burden, recent cerebral ischemic event, and higher NYHA class appear to be the primary determinants of risk.

As during other types of cardiac procedures, periprocedural stroke during TAVI is generally ischemic and embolic.[25] TAVI patients have several high-risk features that make cerebral embolization particularly common. First, the prevalence of severe aortic atherosclerosis increases across grades of AS, which when combined with the large-caliber catheters

necessary for TAVI, make dislodgement of aortic debris more likely.[26] Second, disruption of aortic valvular and annular calcification during TAVI is an additional source of embolic material; procedural transcranial Doppler monitoring indicates that the valve itself is the primary source of cerebral emboli following TAVI, and that most emboli are composed of debris dislodged during direct manipulation of the calcified aortic valve and crushing of the leaflets and aortic annulus during implantation.[27]

4.1.3 **TAVI and Silent Cerebral Ischemia**

In addition to clinical stroke, there is increasing recognition of the importance of subclinical manifestations of periprocedural cerebral embolization in cardiac procedures in general and TAVI in particular.[28-30] A growing body of evidence indicates that clinically silent cerebral ischemia is common after TAVI and may have an important impact on clinical and neurocognitive outcomes.

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a highly sensitive and specific technique to visualize acute ischemia.[31] Acute ischemia presents on DW-MRI as a hyperintense area against the dark background of normal tissue, allowing detection of even small lesions. MRI-based methods have greater sensitivity to detect cerebral infarcts, particularly small lesions, compared with computed tomography (CT) due to stronger field magnets, thinner slices, and different pulse sequences.[32] DW-MRI has an average sensitivity of 94% and specificity of 97% in detecting stroke in humans.[33] It has been used extensively as a surrogate for cerebral embolization after catheter-based and surgical cardiovascular interventions.[31, 34] In addition, standardized endpoint definitions for TAVI trials (VARC-2) include MRI or computed tomographic neuroimaging as an important supplement to the clinical diagnosis of stroke and TIA, as well as a requisite for diagnosing stroke in patients with non-focal global encephalopathy.[35]

Several small studies (Tables 1-4) have reported DW-MRI data after unprotected TAVI. Foci of restricted cerebral perfusion on DW-MRI (cerebral ischemic lesions) are present in approximately 77% of patients (reported range 58% to 93%) after TAVI (Table 1). Most patients have multiple lesions (mean 4.6) (Table 2), distributed bilaterally in a pattern suggesting cerebral embolization. Several studies have reported the volume of single (Table 3) and total per-patient (Tables 4 and 5) lesion volumes after TAVI, with wide variance between studies; the relative degree to which this variation is attributable to methodological and patient-level differences in the extent of affected cerebral tissue is unclear.

Table 1. Reported Incidence of Ischemic Lesions on Post-TAVI DW-MRI

Study	Sample Size (N)	Subjects with Lesions (n)	Proportion with Lesions (n/N)
Arnold 2010[36]	25	17	68%
Astarci 2013[37]†*	44	41	93%
Fairbairn 2012[38]	31	24	77%
Ghanem 2013[39]†	39	28	72%
Kahlert 2010[40] *	32	27	84%
Knipp 2013[41]	12	7	58%
Rodes-Cabau 2011[20]*	60	41	68%
Uddin 2013[42]	45	37	82%
Average	36	28	75%
Weighted Mean	--	--	**77%**

† Multiple publications with overlapping data. Data from the most recent (and largest) reports are provided.
* Data from studies reporting separate results from multiple study arms were pooled.

Table 2. Reported Number of Ischemic Lesions on Post-TAVI DW-MRI

Study	N	Lesion Count				
		Range (min, max)	Mean	SD	Median	IQR [25-75]
Astarci 2013[37]†*	44	--	7.9	--	--	--
Fairbairn 2012[38]	31	--	4.2	6.5	2	1-5
Ghanem 2010[43]‡	22	0, 19	3.4	5.1	1.5	0.25-4
Kahlert 2010[40]*	32	0, 19	3.6	--	--	--
Knipp 2013[41]	12	0, 5	1.8	1.9	1.5	--
Onsea 2012[44]	20	--	7.2	--	--	--
Rodes-Cabau 2011[20]*	60	1, 36	4.2	--	3	2-8
Average	31.5	**0, 20**	**4.6**	--	**2**	**1-6**

† Multiple publications with overlapping data. Data from the most recent (and largest) report is provided.
* Data from studies reporting separate results from multiple study arms were pooled.
‡Multiple publications with overlapping data. Data from the first report were used because patient-level data was provided, allowing calculation of SD, median, and IQR.

Table 3. Reported Single-lesion Volume on Post-TAVI DW-MRI

Study	N	Per Lesion Volume (cm^3)				
		Range (min, max)	Mean	SD	Median	IQR [25-75]
Astarci 2013[37]†*	44	--	0.17	--	--	--
Fairbairn 2012[38]	31	--	0.49	--	--	--
Ghanem 2010[43]‡	22	0, 11.7	0.76	2.47	0.15	0.025-0.33
Kahlert 2010[40]*	32	0.059, 0.094	0.075	--	--	--
Knipp 2013[41]	12	0.015, 1.21	0.172	0.283	--	--
Average	28.2	**0.025, 4.33**	**0.334**	--	**0.15**	--

† Multiple publications with overlapping data. Data from the most recent (and largest) report is provided.
* Data from studies reporting separate results from multiple study arms were pooled.
‡Multiple publications with overlapping data. Data from the first report were used because patient-level data was provided, allowing calculation of SD, median, and IQR.

Table 4. Reported Total Lesion Volume (Per-Subject) on Post-TAVI DW-MRI

Study	N	Per Patient Lesion Volume (cm^3)				
		Range (min, max)	Mean	SD**	Median	IQR [25-75]
Astarci 2013[37]†*	44	--	1.65	--	--	--
Fairbairn 2012[38]	31	--	2.05	3.50	--	--
Ghanem 2010[43]‡	22	0, 70.3	4.3	14.9	0.30	0.025-1.23
Uddin 2013[42]	45	--	1.74	2.8	--	--
Average	36	--	**2.44**	**5.5**	--	--
Weighted Average	--	--	**2.18**	**4.5**	--	--

† Multiple publications with overlapping data. Data from the most recent (and largest) report is provided.
* Data from studies reporting separate results from multiple study arms were pooled.
‡Multiple publications with overlapping data. Data from the first report were used because patient-level data was provided, allowing calculation of SD, median, and IQR for per-patient total lesion volume.
** Average and weighted average Standard Deviations calculated using SD per unit method

Table 5. Reported Total Lesion Volume (Per-Subject) on Post-TAVI DW-MRI - Excluding Subjects Who Experienced a Stroke

Study	N	Per Patient Lesion Volume (cm^3)				
		Range (min, max)	Mean	SD**	Median	IQR [25-75]
Astarci 2013[37]†*	44	--	1.65	--	--	--
Fairbairn 2012[38]¥	29	--	1.1	1.1	--	--
Ghanem 2010[43]‡¥	21	0, 7.8	1.16	2.08	0.30	0-1.00
Uddin 2013[42]	45	--	1.74	2.8	--	--
Average	35	**--**	**1.41**	**2.07**	**--**	--
Weighted Average	--	**--**	**1.49**	**2.18**	--	--

† Multiple publications with overlapping data. Data from the most recent (and largest) report is provided.
* Data from studies reporting separate results from multiple study arms were pooled.
‡Multiple publications with overlapping data. Data from the first report were used because patient-level data was provided, allowing calculation of SD, median, and IQR for per-patient total lesion volume.
** Average and weighted average Standard Deviations calculated using SD per unit method
¥ Strokes excluded where possible (1 subject with a major stroke [Ghanem 2010] and 2 subjects with unspecified stroke [Fairbairn 2012])

The clinical significance of asymptomatic DW-MRI lesions is incompletely characterized. However, in population-based studies the presence of clinically silent brain infarcts has been associated with frailty, declines in physical function, reduced cognitive ability, depressive symptoms, and an increased risk of subsequent stroke or TIA.[32, 45, 46] Several studies have found an association between DW-MRI lesions and neuropsychological deficits after conventional valve surgery,[47, 48] and DW-MRI lesions have also been associated with chemical markers of neuronal damage that in turn correlate with postoperative cognitive deficits and embolic stroke.[49]

Thus far, small studies of DW-MRI lesions after TAVI have failed to detect an association between post-procedural ischemic lesions and risk of future neurological events[36, 50, 51] or measurable impairments of neurocognitive function (using the Mini Mental State Examination).[20, 40, 43, 52] However, concerns remain about the potential impact of even transient and asymptomatic ischemic lesions on long-term cognitive outcomes and other neurological syndromes.[33, 53-57]

DW-MRI studies examining neurocognitive outcomes after TAVI have been exploratory (not powered to detect clinically meaningful neurocognitive changes) and lack long term follow-up. Furthermore, while routine clinical examination can reliably detect focal neurological abnormalities and deficits, more subtle evidence of global neurological dysfunction such as cognitive decline, memory and mood disturbances, reduction of psychomotor speed, and personality changes require specific testing for diagnosis and may be missed. The MMSE, the most frequently used cognitive test in these studies, is relatively insensitive to mild cognitive impairment and declines in non-memory domains.[58] These issues are likely to receive increased attention as the indications for TAVI are expanded to younger populations with increased life expectancy.

4.1.4 **Stroke Assessment- National Institute of Health Stroke Scale- NIHSS**

The NIHSS was first derived by Brott *et al.* to assess stroke severity in a naloxone trial[59] and later modified and utilized in a tPA trial by the NINDS[60]. While the scale has been shown to have prognostic implications[61-64], the timing of conducting the NIHSS assessment and the number of points considered as 'true worsening' differs between trials[65-71]. Previous Cerebral

Embolic Protection Device (CEPD) trials (DEFLECT III[8], EMBOL-X[72], MISTRAL-C[73], and CLEAN-TAVI[74]) have used a cut-off of 1 point (See below).

4.1.5 **Prevention of Periprocedural Cerebral Embolism**

The devastating consequences of periprocedural stroke during TAVI, as well as concern regarding potential long-term neurocognitive sequelae of subclinical cerebral embolic events, have prompted investigation into methods to minimize or prevent periprocedural cerebral embolism during cardiac surgery and endovascular interventions. Because atheromatous and calcific embolic are substantial contributors to cerebral embolism during TAVI, a mechanical means of preventing such material from reaching the cerebral circulation could be an effective approach. Because approximately 50% of TAVI-related neurological events are directly procedure-related,[23] such devices could have a meaningful impact on stroke and other cerebral embolic events in TAVI patients.

The DEFLECT I Trial (NCT01448421) of the first-generation TriGuard cerebral embolic protection device (CEPD) (from which the TriGuard HDH device and the TriGUARD *3* device used in the present study were developed) demonstrated good procedural success and safety, as well as a reduction in total per-patient cerebral ischemic lesion volume after TAVI with embolic protection compared with a historical control of unprotected TAVI.[75]

Table 6. Comparison of Post-TAVI DW-MRI Lesion Data for TAVI Without vs. With Embolic Protection

Parameter	Unprotected TAVI Historical Average	TAVI with Embolic Protection
Incidence of lesions [proportion of patients]	77%	78.6%
Number of lesions [mean (range)]	4.6 (0-36)	5.1±6.1 (0-28)
Single lesion volume [mean (range)]	0.33 (0.075 – 0.76)	0.13±0.13 (0 – 0.47)
Total lesion volume [mean (range)]	2.18±4.5 (1.65 – 4.3) cm^3	0.77±0.96 (0 – 3.94) cm^3
Results of the DEFLECT I trial of the first-generation TriGuard device (n=28 subjects with paired DW-MRI) compared with Historical Average (Tables 1-4 above)		

Thus far, several randomized control trials have addressed the issue of embolic protection device during TAVI.

The DEFLECT III trial[8] included 85 patients and evaluated the efficacy of the TriGuard HDH device. Complete cerebral vessel coverage was achieved in 89% of subjects. Device use was associated with greater freedom from ischemic brain lesions and a shift towards smaller lesion volumes compared to controls. Clinically, device protection afforded better neurocognitive function and numerically lower rates of death and stroke.

The EMBOL-X trial[72] included 30 patients, with half of the patients randomized to protection with the EMBOL-X device (self-expandable mesh placed in the aorta). Protected patients had fewer lesions and the authors reported statistically significant smaller lesion volumes in the supply region of the MCA. No mortality was observed in this trial in both groups.

Mistral- C[73] included 55 patients with 1:1 randomization to protection with the SENTINEL device (2 cone shaped filters placed into the brachiocephalic trunk and the left common carotid artery). Patients with SENTINEL protection had numerically fewer lesions and a

smaller total lesion volume. Neurocognitive deterioration was present in 4% of patients with device protection and 27% of patients without (p=0.017). Mortality was also reduced in the device arm (not statistically significant).

CLEAN-TAVI[74] published in 2016 included 100 patients with 50 patients randomized to device protection with Claret (2 cone shaped filters described above). The trial showed a statistically significant reduction in the number of lesions and total lesion volume in the device arm. Stroke rates were similar between groups and one death occurred in the control group.

Finally, the recently published SENTINEL trial[9] included 119 controls and 242 device patients (including 123 safety patients). Patients in the device arm had smaller lesion volumes and a lower number of lesions. Stroke rates were reduced in the device arm but no difference was noted in neurocognitive function between groups.

* MRI and other clinical results in the trials above were not statistically significant unless otherwise mentioned.

Major trials and their MRI findings are summarized in table 6a. A comparison of the different clinical endpoints assessed in these trials is presented in table 6b.

Table 6a. MRI findings in RCTs using device protection in TAVI.

Trial*	N	Percent of patients with MRI lesions		Median Number of MRI lesions		Median Total Lesion Volume (mm^3)***	
		Device	Control	Device	Control	Device	Control
DEFLECT III[8] 2015	85	78.8%	88.46%	7	4	100.9****	110****
EMBOL-X[72] 2015	30	57.14%	68.75%	1.28**	2**	--	--
MISTRAL-C[73] 2016	65	72.73%	86.67%	--	--	95	197
CLEAN TAVI[74] 2016	100	97.96%	97.78%	5	10	205	472
SENTINEL[9] 2017	363	--	--	3	5	294	309.8

* Based on published results where available. CLEAN-TAVI results of number of lesions and volume were statistically significant.
** Unclear calculation methodology in the paper.
*** Total lesion volume in all territories
**** Results by per treatment.

Table 6b. Clinical endpoints in RCTs using device protection in TAVI

Trial	N	Death at 30 days		Stroke at 30 days		Any worsening NIHSS	
		Device	Control	Device	Control	Device	Control
DEFLECT III[8] 2015	85	2.17%	5.13%	4.35%	5.13%	3.8%*	4.5%*
EMBOL-X[72] 2015	30	0%	0%	--	--	3.8%*	4.5%*
MISTRAL-C[73] 2016	65	3.12%	9.09%	0%	6.06%	0%**	5%**
CLEAN TAVI[74] 2016	100	0%	2%	8%	8%	17.9%*	22.5%*
SENTINEL[9] 2017	363	1.28%	1.8%	5.63%	9.09%	--	--

* At 30 days
** At discharge, data from presentation at TCT 2015, not presented in published paper.

4.1.6 **Study Population- Minorities**

CEPD trials enrolled patients referred for TAVI, hence patient demographics are similar to current TAVI enrollment practices. Table 6c summarizes the distribution of age and sex in current CEPD trials. Racial disparities in TAVI have been previously reported[76]. Race was not reported in the above-mentioned CEPD trials but is expected to reflect rates similar to TAVI trials. In this trial sites will be encouraged to enroll minorities.

Table 6c. Sex and age distribution in current CEPD trials.

Trial	N	Age (years) mean±SD *or* median (IQR)		Female N(%)	
		Device	Control	Device	Control
DEFLECT III[8] 2015	85	82.5±6.5	82.3±6.0	56.5%**	48.7%**
EMBOL-X[72] 2015	30	81.0±5.0	82.1±4.1	10 (71.4%)	8 (50.0%)
MISTRAL-C[73] 2016	65	82 (79-84)	82 (77-86)	15 (47%)	16 (49%)
CLEAN TAVI[74] 2016	100	80.0±5.1	79.3±4.1	29 (58%)	28 (56%)
SENTINEL[9] 2017	240*	85.0 (78.4-89.4)	83.1 (77.2-87.2)	58 (48.7%)	63 (52%)

* Safety population not included
** N not reported

4.2 Rationale

The incidence of stroke and subclinical cerebral ischemic lesions, and their association with post-procedural neurological deficits, indicate that methods to prevent or reduce cerebral embolization are vital to optimizing TAVI procedures and improving the outcomes of patients with severe aortic stenosis. The first-generation TriGuard device has been demonstrated to safely reduce the total cerebral ischemic lesion volume after TAVI compared with historical controls. This prospective, randomized trial will provide more comprehensive evaluation of the safety and efficacy of the TriGuard HDH and TriGUARD *3* devices compared with a concurrent active control of unprotected TAVI.

By employing standardized image acquisition and analysis parameters and detailed neurological testing, the REFLECT trial will also advance the understanding of subclinical neurological events and their relationship with neurocognitive function in patients undergoing cardiovascular interventions.

4.3 Device Description

The following is a summary description of the Investigational Devices. For additional information, please refer to the Instructions for Use.

4.3.1 **Devices Summary**

4.3.1.1.1 Phase I- TriGuard HDH

The Keystone Heart TriGuard HDH CEPD (Figure 1) is a temporary, sterile, single use, biocompatible filter, introduced transfemorally through a 9F sheath to the aortic arch. Under fluoroscopic guidance, the device is positioned in the aortic arch to cover all 3 major cerebral arteries (innominate, left carotid, and subclavian arteries), and is held in position by an atraumatic stabilizer in the innominate artery (Figure 2). Once the device is in position, emboli and particulate matter are diverted away from the cerebral circulation and downstream to the descending aorta, where they are either harmless or can be treated effectively.

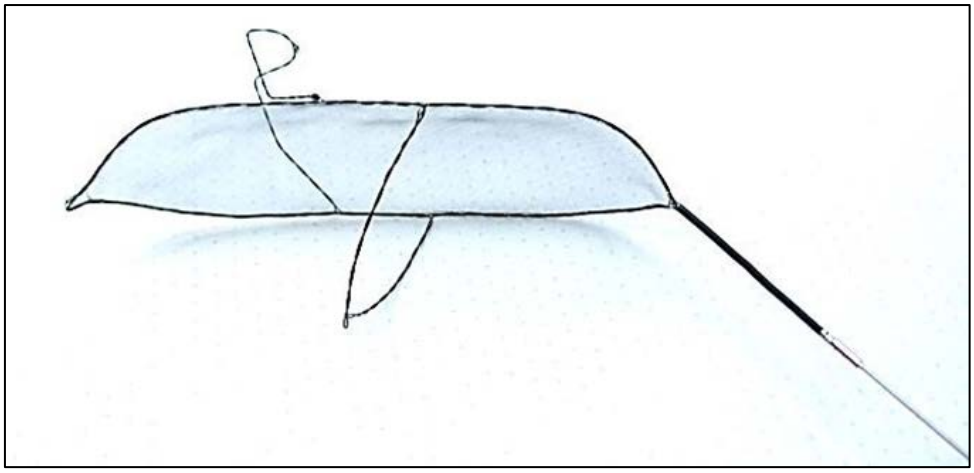


Figure 1. The TriGuard HDH CEPD

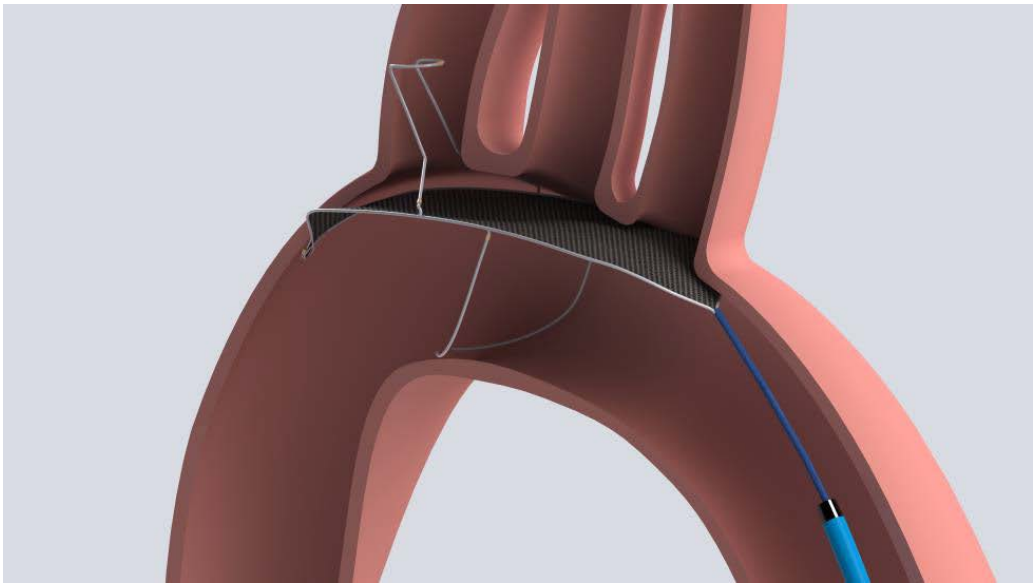


Figure 2. TriGuard HDH device positioning in the aortic arch.

The TriGuard HDH CEPD is available in a single size, and is composed of a structural nitinol frame, lower stabilizer legs that push it towards the upper wall of the aortic arch, an upper stabilizer that protrudes into the innominate artery ostium, and a nitinol mesh. The frame includes 4 radiopaque markers to increase CEPD visualization under fluoroscopy, and ends in a 60 mm tail comprised of braided nitinol wires with a Duraskin™-coated coil on top of it. A connector with 180° of rotational freedom connects the CEPD frame to the delivery tether.

The CEPD filter consists of a thin and durable nitinol mesh (nominal pore size 130 X 250 µm) attached to the frame, allowing maximal blood flow while diverting clinically significant emboli toward the descending aorta. The CEPD is heparin coated to reduce thrombogenicity and increase lubricity. The chemical and physical properties of this immobilized, biocompatible, hydrophilic, ultrathin polymeric coating reduce the likelihood of blood component adherence and activation, reducing the formation of thrombi or emboli.

The CEPD filter unit is connected to a delivery tether that serves for pushing, maintaining and retrieving the filter from the aortic arch. In addition to the filter, the TriGuard System includes a delivery subsystem for crimping and loading the device into commercially-available 7F and

9F sheaths (please refer to the TriGuard HDH Instructions for Use for a listing of compatible introducer sheaths).

Device deployment is accomplished by pre-loading (crimping) the CEPD through the dedicated crimper into the distal end of a commercially-available 7F sheath delivery system. Under fluoroscopy, the 7F sheath is pushed via a commercially-available 9F sheath delivery system, already inserted through a femoral artery access site. The device is then de-sheathed into the 9F introducer and the 7F introducer is removed.

4.3.1.1.2 Phase II- TriGUARD *3* CEPD

The Keystone Heart TriGUARD *3* CEPD (Figures 1a, 1b and 2a) is a temporary, retrievable, sterile, single use, biocompatible filter, introduced transfemorally through an 8F sheath to the aortic arch. Under fluoroscopic guidance, the device is positioned in the aortic arch (Figure 2a) to cover all 3 major cerebral arteries (covering the innominate, left carotid, and left subclavian arteries), and is held in position by the device's circumferential pressure and the support of the nitinol shaft (external communicating device) in the aortic arch. Once the device is in position, emboli and particulate matter are diverted away from the cerebral circulation and downstream to the descending aorta, where they are either harmless or can be treated effectively.

The TriGUARD *3* CEPD is available in a single size, and is composed of a structural nitinol frame that pushes it towards the upper wall of the aortic arch, and a Polymer mesh. The frame is radiopaque to increase device visualization under fluoroscopy. A nitinol connector connects the device frame to the delivery system.

The CEPD filter consists of a thin and durable Polymer mesh (nominal pore size 115 X 145 µm) attached to the frame, allowing maximal blood flow while diverting clinically significant emboli toward the descending aorta. The filter is heparin coated to reduce thrombogenicity and increase lubricity. The chemical and physical properties of this immobilized, biocompatible, hydrophilic, ultrathin polymeric coating reduce the likelihood of blood component adherence and activation, reducing the formation of thrombi or emboli.

The CEPD filter unit is connected to a delivery system that serves for pushing, maintaining and retrieving the filter from the aortic arch. In addition to the filter, the TriGUARD *3* System includes a delivery subsystem for crimping and loading the device into a commercially available 8F braided sheath.

Device deployment is accomplished by pre-loading (crimping) the CEPD through the dedicated crimper into the distal end of the 8F delivery system. Under fluoroscopy, the 8F sheath is advanced over the wire already inserted through a femoral artery access site. The device is then de-sheathed and exposed to the blood stream.

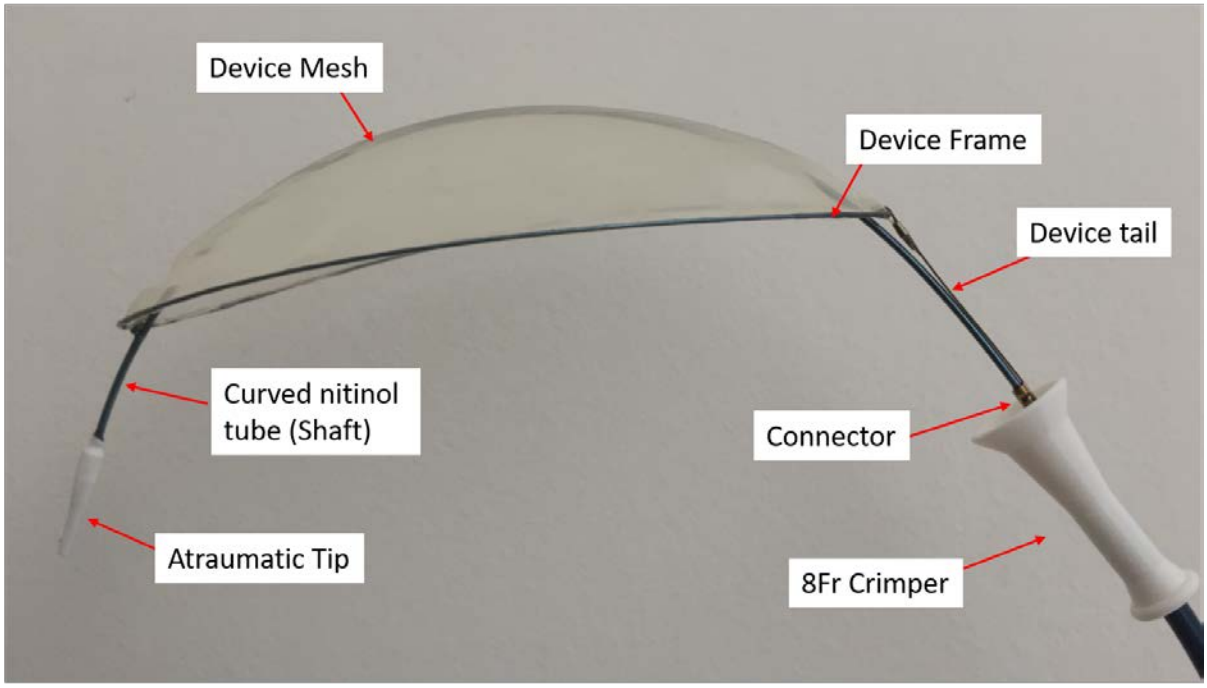


Figure 1a. The TriGUARD *3* CEPD

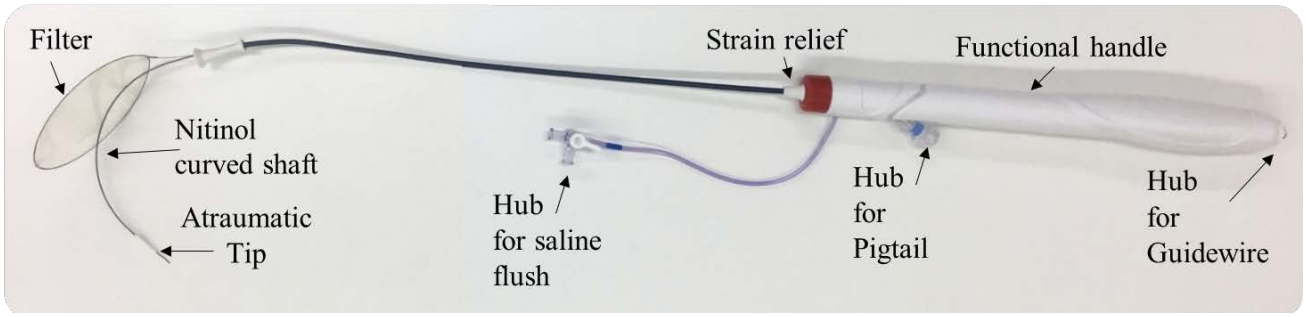


Figure 1b. TriGUARD *3* system overview.

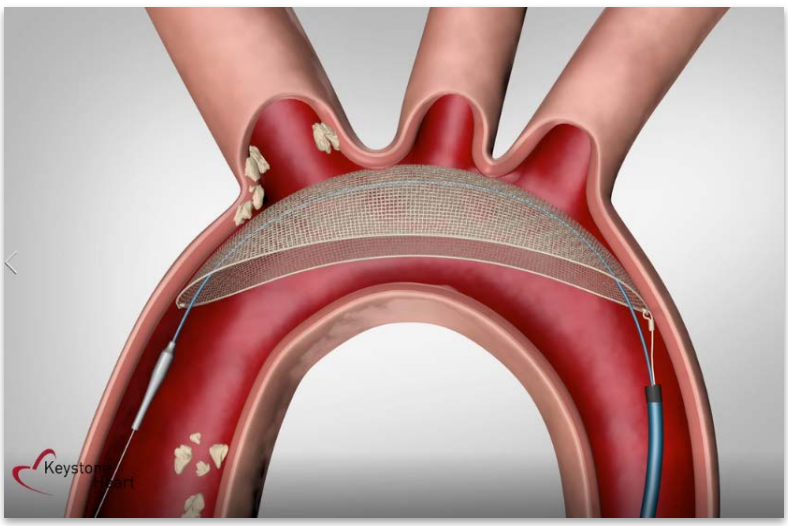


Figure 2a. TriGUARD *3* device positioned in the aortic arch

4.3.2 **Regulatory Status**

The TriGuard HDH has received CE Mark and is commercially available in Europe and Israel. Use of the device at European and Israeli sites in the REFLECT study is in accordance with its market approved use.

In the United States, the TriGuard HDH and the TriGUARD *3* are for investigational use only.

4.3.3 **Device Packaging**

4.3.3.1.1 Phase I- TriGuard HDH

The device is supplied pre-assembled in a single rigid inner blister tray (Figure 3) containing the TriGuard HDH CEPD, a 9F delivery sheath extension (including a loading tube with a double hemostasis valve), a crimper (to load the CEPD into the delivery system), and Instructions for Use. The inner blister tray is placed in a sterility barrier consisting of a thermoformed blister tray with a Tyvek lid, which is placed in a cardboard box. The entire package is sterilized using Gamma irradiation.

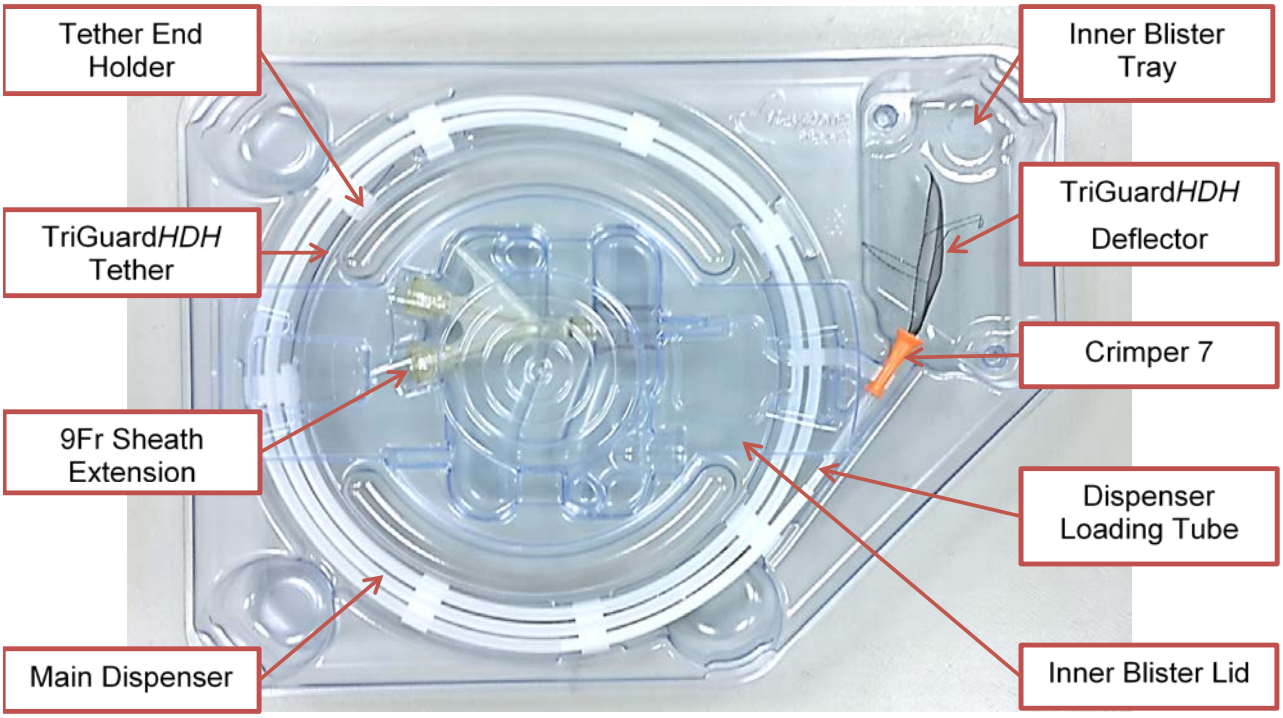


Figure 3. The TriGuard HDH System

4.3.3.1.2 Phase II- TriGUARD *3*

The device is supplied pre-assembled in a single rigid blister tray (Figure 3a) containing the TriGUARD *3* CEPD filter, a crimper (to load the filter into the delivery system), and Instructions for Use. The inner blister tray is placed in a sterility barrier consisting of a thermoformed sealed Tyvek pouch, which is placed in a cardboard box. The entire package is sterilized using EtO.

Figure 3a. TriGUARD *3* System Packaging

4.3.4 **Comparison between Device Generations**

The TriGuard HDH device and the TriGUARD *3* device share the same basic principles of operation and intended use and are manufactured under the same Quality System. Design changes between the TriGuard HDH and TriGUARD *3* are expected to improve device safety, effectiveness, performance, and ease of use (Table 6d) and will be tested in Phase II.

In comparison with TriGuard HDH system, the TriGUARD *3* system includes the following design changes:

- A simplified self-positioning, self-stabilizing frame design that utilizes circumferential pressure and the support of the nitinol delivery shaft to improve vessel wall apposition and eliminate the need for dedicated stabilizer elements in the innominate artery and aortic arch, improving device safety, particle deflection efficacy, and ease of deployment and positioning. In addition, the revised device design permits the use of cerebral protection in a broader anatomic subset of patients because it is not limited by aortic arch or innominate artery ostium diameter or the presence of calcification, atheroma, or tortuosity in the innominate artery.
- Reduced filter mesh pore size (115 × 145 µm vs. 130 × 250 µm) for deflection of smaller particles, achieved via a different mesh material (Polymer vs. nitinol);
- An increased filter area of 68.3 cm^2 vs. 20.9 cm^2.
- A frame that is fully visible via fluoroscopy (eliminating the need for radiopaque marker bands) for improved monitoring during deployment and positioning; and
- A refined delivery subsystem that reduces the delivery profile (8 F vs. 9 F) expected to improve safety, reduce the number of procedural steps required for deployment, and allow over-the-wire introduction and positioning for better ease of use.

Table 6d. Comparison between devices

TriGuard HDH	TriGUARD *3*
Nitinol frame with upper and lower stabilizers	Self-positioning, self-stabilizing nitinol frame, fully visible via fluoroscopy
Nitinol mesh (pore size 130 x 250 µm)	Polymer mesh (pore size 115 x 145 µm)
Filter area = 20.9 cm^2	Filter area = 68.3 cm^2
9 Fr delivery	8 Fr OTW delivery

4.3.5 **Intended Use**

The Keystone Heart TriGuard™ HDH and TriGUARD *3* are aortic CEPDs designed to reduce the amount of embolic material that may enter the cerebral blood circulation during transcatheter heart valve replacement or implantation.

5.0 Study Design

5.1 Study Design Change and Rationale

REFLECT Version 10.0 was a prospective, single-blind, randomized, multicenter safety and efficacy trial. The study was intended to enroll up to 355 subjects and up to 90 roll-ins. Enrollment in this cohort (termed Phase I in this protocol version) was halted after 204 subjects were randomized and 54 roll-ins were enrolled) based on a recommendation of the DSMB following interim data review at the prespecified interm analysis timepoint. A next iteration device (TriGUARD *3*) designed for increased efficacy, ease of use, and improved safety will be tested in Phase II.

5.1.1 **Rationale for Phase II**

This amendment to the protocol is intended to allow the evaluation of the TriGUARD *3*. This next iteration of the device will be the only manufactured and available TriGuard device.

The proposed modifications to the ongoing REFLECT trial will allow a scientifically valid evaluation of the safety, effectiveness, and performance of the TriGUARD *3* device by leveraging the engagement of existing US sites and operators who are familiar with the prior generation device, as well as blinded clinical data already collected from Phase I control patients. This approach will minimize the total number of study subjects exposed to any risks associated with the investigational device, maximize the value of the contributions of subjects already enrolled in the trial, and potentially speed market availability of the TriGUARD *3* device.

Analysis will include poolability assessment and data validity of the old controls with the new ones and between sites in US and OUS as detailed in the SAP.

5.2 Study Design Overview

This study is a prospective, single-blind, three arm, randomized (2 device: 1 control), multicenter safety and efficacy trial designed to enroll up to 603 evaluable subjects in two consecutive phases: Phase I, which evaluated the TriGuard HDH device enrolled 258 subjects (including 54 Roll-Ins) prior to enrollment suspension at the recommendation of the independent DSMB following an interim data review at the prespecified interim analysis time point. Phase II will enroll up to 345 subjects (including up to 50 Roll-Ins) and will utilize the TriGUARD *3* (Figure 3b shows the patient flow/disposition).

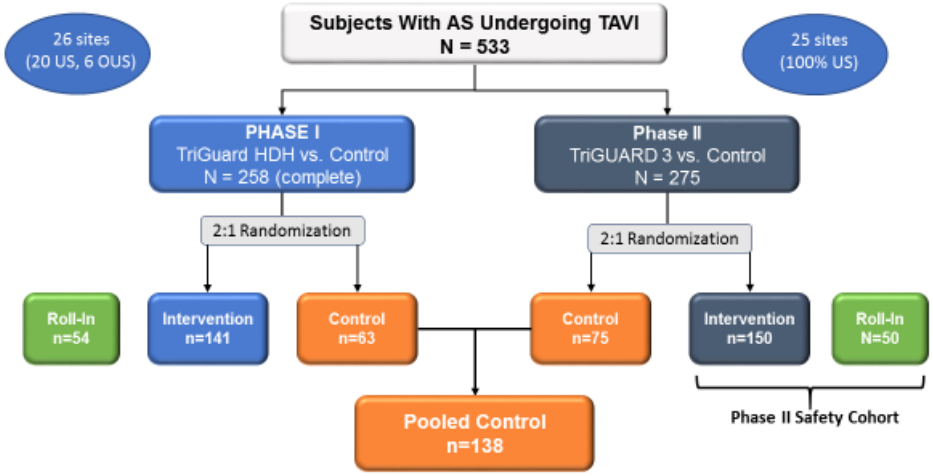


Figure 3b. REFLECT Phase I and Phase II Trial Design (Note: The depicted Phase II design reflects the sample size of the initial randomized cohort, not including a possible adaptive design sample size increase)

Phase I:

In phase 1, a total of 204 evaluable subjects and 54 roll-in subjects were enrolled at 26 total investigational sites in the United States, Europe, and Israel, including 20 sites in the United States. A minimum of 50% of subjects were planned to be enrolled at US sites, and no single site was permitted to enroll more than 20% of all subjects.

Subjects with indications for TAVI and who meet study eligibility criteria were randomized 2:1 (stratified by study site) to one of two treatment arms:

- **Intervention (Phase I Cohort)** – TAVI with the TriGuard HDH CEPD
- **Control** – standard unprotected TAVI

At sites where the investigator did not have prior experience with the TriGuard device (minimum of 2 prior cases), up to 3 roll-in subjects were enrolled. Roll-in subjects were not randomized, but underwent TAVI with the TriGuard HDH device. These cases were proctored by a Sponsor representative. Investigational sites with ≥2 prior TriGuard cases were allowed to enroll 1 roll-in subject at the discretion of the site principal investigator.

All subjects were to be followed clinically in-hospital and at 30 and 90 days, undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and undergo neurologic and neuropsychological testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 and 90 days.

The initial randomized cohort was planned to enroll up to 285 subjects.

Note: Enrollment in Phase I has been halted after enrolling a total of 258 subjects (54 roll-ins and 204 randomized subjects including 63 controls) based on a recommendation of the DSMB following interim data review at the prespecified interm analysis timepoint. A new generation device designed for increased efficacy, ease of use, and improved safety which will be tested in Phase II (below).

Phase II

In Phase II, up to 295 randomized subjects and 40-50 roll-in subjects will be enrolled at up to 25 sites in the United States (inclusive of sites enrolling subjects in Phase I). No single site will be permitted to enroll more than 20% of all randomized subjects in Phase II.

Subjects with indications for TAVI and who meet study eligibility criteria will be randomized 2:1 (stratified by study site) to one of two treatment arms:

- **Intervention** – TAVI with the TriGUARD *3* CEPD
- **Control** – standard unprotected TAVI**.**

Randomization will be stratified by implanted valve type (Medtronic vs. Edwards).

No single valve type will be implanted in more than approximately 70% of randomized patients (phase II).

Roll-in subjects (a minimum of 2 and a maximum of 3 Roll-ins per-site) will not be randomized, but will undergo TAVI with the TriGUARD *3* device. These cases will be proctored by a Sponsor representative.

All subjects will be followed clinically in-hospital and at 30 days, undergo diffusion-weighted MR imaging 2 to 5 days post-procedure, and undergo neurologic (NIHSS) testing pre-procedure, post-procedure (2-5 days post-procedure), and at 30 days. A follow-up phone-call to assess the occurrence of death or stroke will be done at 90 days.

The initial randomized cohort will consist of up to 225 subjects. After at least 50% of the initial randomized cohort (approximately 112 subjects) have reached the 30 day primary efficacy endpoint evaluation time point, a sample size re-estimation will be performed in case the conditional power of the trial (assessed by the independent biostatistician) is >40% but <80%, subject to approval by the Sponsor. If this analysis determines that more than 225 randomized subjects will be required to ensure adequate study power, enrollment may continue until the required number of subjects have been enrolled, or until the total subject limit for the study has been reached (whichever occurs first).

5.3 Study Objectives

The objective of the REFLECT trial is to evaluate the safety and efficacy of the TriGuard HDH and TriGUARD *3* CEPDs in patients TAVI, in comparison with an active control group of patients undergoing unprotected TAVI.

The study will also report additional secondary safety, efficacy, and performance endpoints evaluating the TriGuard HDH and TriGUARD *3* in patients undergoing transcatheter aortic valve implantation (TAVI) in comparison with patients undergoing unprotected TAVI. Other measures related to the effect of embolic protection on TAVI procedural time and radiation exposure will also be collected.

5.4 Study Endpoints

5.4.1 **Primary Endpoints**

5.4.1.1.1 Primary Safety Endpoint

The primary safety endpoint of the study is **combined safety** at 30 days, defined according to modified VARC-2 [1] (“TAVI early safety”) as the composite of:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening or disabling bleeding
- Acute kidney injury – Stage 2 or 3 (including renal replacement therapy)
- Coronary artery obstruction requiring intervention

- Major vascular complication
- Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)

5.4.1.1.2 Primary Efficacy Endpoint- **Phase II**

The primary efficacy endpoint of the study is the **hierarchical composite efficacy endpoint**, determined by pair-wise comparisons among all subjects according to the following pre-specified hierarchy of adverse outcomes:

- All-cause mortality and/or any stroke (fatal and non-fatal, disabling or non-disabling) [evaluated at 30 days]
  - If both had a death/stroke, a time to event analysis by days will determine a win
  - If both patients had a stroke at the same day the comparison moves to the next tier
- NIHSS worsening (increase from baseline) [evaluated at 2 to 5 days post-procedure]
- Freedom from any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure.

Each subject in the intervention group will be compared with each and every subject from the control group based on the above hierarchy according to the Finkelstein-Schoenfeld method.[2] For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or both have a stroke on the same day, it is equilibrium (score 0). If both subjects survive free of stroke to 30 days, the comparison moves to the next tier of the hierarchy. A lack of an event is given a +1 score. An event which is less severe than the comparison gets a 0 score (for example death vs. stroke)

After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared.

5.4.2 **Secondary Endpoints**

5.4.2.1.1 Hypothesis-driven secondary endpoints

For the following secondary endpoints, a test for superiority of each intervention group to the control group will be performed. To address the issue of multiple tests among these secondary endpoints, sequential testing is planned. Secondary endpoints will be formally tested if and only if the primary study hypotheses are confirmed. The secondary endpoints will be tested individually, in the order in which they are listed as follows:

- **All stroke** [evaluated at 7 days in the eITT population]
- **NIHSS worsening**, defined as any NIHSS score increase from baseline [evaluated at 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]. A sensitivity analysis will further compare $\geq$2 points NIHSS worsening [evaluated at 2-5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]
- **Composite of all-cause mortality and all stroke** [evaluated at 7 days in the eITT population]

- **CNS Infarction** (NeuroARC defined) [evaluated at 30 days in the eITT analysis population]
- **Total volume of cerebral ischemic lesions** detected by DW-MRI, [evaluated 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

The above endpoints will be tested by this pre-specified sequence, until the first non-significant difference is found between the two treatment groups. After that, other treatment comparisons will be examined in an exploratory manner.

5.4.2.1.2 Secondary Safety Endpoints

The following safety endpoints will be evaluated in-hospital and at 30 days. Overall event rates will be reported by treatment group. In the Intervention and Roll-In groups, all safety endpoints will be adjudicated for their relationship to the investigational device and/or the investigational procedure by an independent Clinical Events Committee (§11.1):

- In-hospital procedural safety, defined as the composite of the following Major Adverse Cardiovascular and Cerebrovascular Events (MACCE):
  - All-cause mortality
  - All stroke (disabling and non-disabling)
  - Life threatening (or disabling) bleeding
  - Acute kidney injury – Stage 2 or 3 (including renal replacement therapy)
  - Major vascular complications
- TAVI device success (VARC), evaluated in-hospital, defined as:
  - Absence of procedural mortality AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
  - Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (VARC-defined) and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation (VARC-defined) (site-reported)
- General safety, defined as the composite of the following adverse events (each VARC-2 defined):
  - All-cause mortality
  - All stroke (disabling and non-disabling)
  - Acute kidney injury – Stage 3 (including renal replacement therapy)
- Mortality [evaluated in-hospital and at 30 and 90 days]:
  - All-cause mortality
    - Cardiovascular mortality

        - Neurologic event related mortality
    - Non-cardiovascular mortality
- Myocardial infarction:
  - Peri-procedural MI (≤72 hours after the index procedure)
  - Spontaneous MI (>72 hours after the index procedure)
- Neurological Events (component and composite):
  - Stroke (VARC-2 defined) **[evaluated in-hospital and at 30 and 90 days]**
    - Ischemic stroke
    - Hemorrhagic stroke
    - Undetermined
  - Disabling Stroke (VARC-2 defined) **[evaluated in-hospital and at 30 and 90 days]**
  - Non-disabling stroke (VARC-2 defined) **[evaluated in-hospital and at 30 and 90 days]**
  - Transient ischemic attack (TIA) (VARC-2 defined)
  - Overt CNS Injury (NeuroARC defined Type 1) **[evaluated in-hospital and at 30 and 90 days]**
  - Covert CNS Injury (NeuroARC defined Type 2)
  - Neurological dysfunction without CNS injury (NeuroARC defined Type 3)
  - CNS infarction (NeuroARC defined composite neurological endpoint)
  - CNS hemorrhage (NeuroARC defined composite neurological endpoint)
- Bleeding Complications:
  - Life-threatening bleeding (VARC-2)
  - Major bleeding
  - Minor bleeding
- Acute Kidney Injury (AKIN Classification):
  - Stage 2
  - Stage 3
- Vascular Complications:
  - Major vascular complications
  - Major vascular complications related to device

5.4.2.1.3 Secondary Efficacy Endpoints

5.4.2.1.4 Phase I: Hierarchical composite efficacy endpoint, determined by pair-wise comparisons among all subjects according to the following pre-specified hierarchy of adverse outcomes:

- All-cause mortality or any stroke (disabling or non-disabling) [evaluated at 30 days]
- NIHSS worsening (increase from baseline) [evaluated at 2-5 days post-procedure] or Montreal Cognitive Assessment worsening (decrease of 3 or more points from baseline) [evaluated at 30 days]
- Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure

Each subject in the intervention group will be compared with each and every subject from the control group based on the above hierarchy according to the Finkelstein-Schoenfeld method.[2] For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke, it is equilibrium (score 0). If both subjects survive free of stroke to 30 days, the comparison moves to the next tier of the hierarchy.

After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared.

5.4.2.1.5 Imaging Efficacy Endpoints (Phase I and Phase II):

- Presence of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Number of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Per-patient average single cerebral ischemic lesion volume detected by DW-MRI, evaluated 2 to 5 days post-procedure
- Single cerebral ischemic lesion volume (lesion-level analysis) detected by DW-MRI, evaluated at 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by DW-MRI, evaluated 2 to 5 days post-procedure

5.4.2.1.6 Neurologic Efficacy Endpoints (Phase I and Phase II):

- NIHSS worsening, defined as an NIHSS score increase from baseline [baseline score compared with score evaluated at 2-5 days post-procedure and at 30 days]
- New neurologic impairment, defined as an NIHSS score increase from baseline accompanied by the presence of cerebral ischemic lesions [evaluated at 2-5 days post-procedure and at 30 days]

5.4.2.1.7 Secondary Performance Endpoints

The following performance endpoints will be evaluated post-procedure in the Intervention group (Roll-Ins excluded). TriGuard HDH and TriGUARD *3* reported individually:

- Successful device deployment, defined as ability to access the aortic arch with the TriGuard HDH or TriGUARD *3* delivery catheter and deploy the device from the delivery catheter into the aortic arch
- Successful device positioning, defined as ability to position the TriGuard HDH or TriGUARD *3* device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by fluoroscopy) until the following time points:
  - Final deployment of the first prosthetic valve
  - Final procedure (after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed)
- Extent of cerebral artery coverage will be reported as:
  - Complete (coverage of all 3 cerebral artery branches)
  - Partial (coverage of 1-2 cerebral artery branches)
  - None

Note: Maintenance of device positioning to each time point and extent of cerebral artery coverage will be evaluated by the Angiographic Core Laboratory.

- Device interference, defined as interaction of the TriGuard HDH or TriGUARD *3* device with the TAVI system leading to:
  - Inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR
  - Inability to deploy the TAVI valve prosthesis, OR
  - Inability to retrieve the valve prosthesis or delivery system
- Successful device retrieval, defined as ability to retrieve the TriGuard HDH or TriGUARD *3* CEPD.
- Technical success, defined as successful device deployment, device positioning, and successful device retrieval in the absence of device interference
- Procedure success, defined as technical success in the absence of any investigational device-related or investigational procedure-related in-hospital procedural safety events

5.4.3 **Other Measures**

The following additional measures will also be evaluated (TriGuard HDH and TriGUARD *3* reported individually):

5.4.3.1.1 **Device deployment time** − Time elapsed between insertion of the TriGuard HDH or TriGUARD *3* device into the groin access point and successful device deployment [evaluated post-procedure]

5.4.3.1.2 **Total procedural time** − Time elapsed between first arterial access and removal of the last catheter from the arterial access sheath [evaluated post-procedure]

5.4.3.1.3 **Total fluoroscopy time** [evaluated post-procedure]

5.4.3.1.4 **Total contrast utilization** [evaluated post-procedure]

6.0 Study Conduct

6.1 Enrollment Criteria

6.1.1 General Inclusion Criteria

Subjects must meet ALL of the following criteria to be eligible for enrollment into the study:

6.1.1.1.1 The patient is a male or non-pregnant female ≥18 years of age

6.1.1.1.2 The patient meets indications for TAVI

6.1.1.1.3 The patient is willing to comply with protocol-specified follow-up evaluations

6.1.1.1.4 The patient, or legally authorized representative, has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the appropriate Institutional Review Board (IRB) or Ethics Committee (EC)

6.1.2 General Exclusion Criteria

Potential subjects will be excluded if ANY of the following criteria apply:

6.1.2.1.1 Patients undergoing TAVI via the trans- apical, trans -axillary, trans-subclavian, or trans-aortic route (applicable to Phase II)

6.1.2.1.2 Patients undergoing TAVI via the transapical approach due to friable or mobile atherosclerotic plaque in the aortic arch (*Phase I only*)

6.1.2.1.3 Patients with a previously implanted prosthetic aortic valve (i.e., planned valve-in-valve TAVI)

6.1.2.1.4 Pregnant or nursing subjects and those who plan pregnancy in the period up to 1 year following index procedure. Female subjects of child-bearing potential must have a negative pregnancy test done within 14 days prior to index procedure per site standard test.

6.1.2.1.5 Patients with known diagnosis of acute myocardial infarction (AMI) within 72 hours preceding the index procedure (according to definition) or AMI >72 hours preceding the index procedure, in whom CK and CK-MB have not returned to within normal limits at the time of procedure, or patients who are currently experiencing clinical symptoms consistent with new-onset AMI, such as nitrate-unresponsive prolonged chest pain.

6.1.2.1.6 Patients with a history of bleeding diathesis or coagulopathy or patients in whom anti-platelet and/or anticoagulant therapy is contraindicated, patients who will refuse transfusion, or patients with an active peptic ulcer or history of upper gastrointestinal (GI) bleeding within the prior 3 months.

6.1.2.1.7 Patients with known mental or physical illness or known history of substance abuse that may cause non-compliance with the protocol, confound the data interpretation, or is associated with a life expectancy of less than one year

6.1.2.1.8 Patients with severe allergy to heparin or known hypersensitivity or contraindication to aspirin, heparin/bivalirudin, clopidogrel, nitinol, stainless steel alloy, and/or contrast sensitivity that cannot be adequately pre-medicated

6.1.2.1.9 Patients with a history of a stroke or transient ischemic attack (TIA) within the prior 6 months

6.1.2.1.10 Patients with renal failure (estimated Glomerular Filtration Rate [eGFR] <30 mL/min, calculated from serum creatinine by the Cockcroft-Gault formula or MDRD- Modification of Diet in Renal Disease formula)

6.1.2.1.11 Patients with hepatic failure (Child-Pugh class C)

6.1.2.1.12 Patients with hypercoagulable states that cannot be corrected by additional periprocedural heparin

6.1.2.1.13 Patients presenting with cardiogenic shock at the time of the index procedure

6.1.2.1.14 Patients with severe peripheral arterial, abdominal aortic, or thoracic aortic disease that precludes delivery sheath vascular access

6.1.2.1.15 Patients in whom the aortic arch (*Phase I and II*), innominate artery ostium (*Phase I only*), or proximal innominate artery (*Phase I only*) are heavily calcified, severely atheromatous, or severely tortuous

6.1.2.1.16 Patients with an innominate artery ostium diameter <10 mm or >25 mm (*Phase I only*)

6.1.2.1.17 Patients with a transverse aortic diameter >43 mm (*Phase I only*)

6.1.2.1.18 Patients with anatomic irregularities of the innominate artery that could prevent positioning of the TriGuard upper stabilizer and compromise stability of the device (*Phase I only*)

6.1.2.1.19 Patients with any other condition that would prevent adherence to the TriGuard HDH (Phase I) or TriGUARD *3* (Phase II) Instructions for Use

6.1.2.1.20 Patients with contraindication to cerebral MRI

6.1.2.1.21 Patients who have a planned treatment with any other investigational device or procedure during the study period

6.1.2.1.22 Patients planned to undergo any other cardiac surgical or interventional procedure during the TAVI procedure (e.g., concurrent coronary revascularization) or within 10 days prior to the TAVI procedure. NOTE: Diagnostic cardiac catheterization is permitted within 10 days prior to the TAVI procedure.

6.2 Subject Enrollment

6.2.1 **Screening and Enrollment**

Patients meeting indications for TAVI will be pre-screened for study eligibility by a member of the research team, including a review of the patient's medical history and any existing diagnostic imaging testing that has been performed as a part of the patient's normal medical care.

Based on the results of pre-screening, potentially eligible patients will be asked to provide written informed consent. Informed consent must be documented prior to the performance of any study-specific screening procedures or assessments. Following receipt of informed consent, a baseline screening assessment will be conducted to verify eligibility; the required documentation must also be provided to the Patient Review Committee (§11.1) to determine anatomic eligibility for the trial.

The patient will be considered enrolled in the study when all the following criteria have been met:

- The patient has provided written informed consent
- Baseline screening has been conducted and:
    - The Patient Review Committee has determined that the patient meets the evaluated anatomic eligibility criteria (based on imaging analysis by independent CT core laboratory) AND
    - The investigator has determined that the patient meets all applicable remaining inclusion and no exclusion criteria
- The point of enrollment has been reached:
    - **For evaluable subjects** (Intervention and Control groups), the point of enrollment is the moment of randomization. Randomization will occur:
        - Within 72 hours prior to the scheduled initiation of the TAVI procedure AND
        - After the investigator has confirmed the subject meets all anatomic eligibility criteria
    - **For Roll-In subjects**, the point of enrollment is the introduction of the TriGuard HDH or TriGUARD *3* device into the bloodstream.

A screening log will be completed to document the enrollment and subject number, or reason for non-enrollment of subjects screened but not enrolled in the study. All enrolled subjects are required to complete all assigned follow-up assessments. No single site was permitted to enroll more than 20% of the total number of evaluable subjects (i.e., no single site may enroll more than 57 evaluable subjects in the initial randomized cohort [in addition to any roll-in subjects] in Phase I, and no more than 45 randomized subjects in the initial randomized cohort [in addition to any roll-in subjects] in Phase II.

Randomization will be stratified by implanted valve type (Medtronic vs. Edwards).

No single valve type will be implanted in more than approximately 70% of randomized patients (phase II).

After at least 50% of the patients in the initial randomized cohort (approximately 112 subjects) have reached the 30 day primary efficacy endpoint evaluation time point, a sample size reestimation will be performed in case the conditional power of the trial (assessed by the independent biostatistician) is >40% but <80%, subject to approval by the Sponsor. If this analysis determines that more than 225 randomized subjects will be required to ensure adequate study power, enrollment may continue until the required number of subjects have been enrolled, or until the total subject limit for the study has been reached (whichever occurs first).

6.2.2 **Roll-In Subjects**

Sites will enroll a minimum of 2 and a maximum of 3 Roll-In subjects. Roll-In subjects will not be randomized to a treatment arm, but will undergo TAVI with the TriGUARD *3* CEPD and will undergo all protocol-specified follow-ups. These cases will be proctored by a Sponsor representative.

For the purposes of analysis, a subject is considered enrolled in the Roll-In phase of the study when:

- The patient has been judged to meet all inclusion and no exclusion criteria (including approval by the PRC), and has signed a Patient Informed Consent form
- The TriGuard HDH or TriGUARD *3* device has been introduced into the patient's bloodstream

6.2.3 **Withdrawal and Replacement of Patients**

Subjects can withdraw from the study at any time; the reason(s) for withdrawal (if given) will be documented. All data available at the time of withdrawal (if any) will be used for analysis. There will be no further follow-up (per this study protocol) on a subject who has withdrawn. Subjects who withdraw from the study will not be replaced. The withdrawal of a subject can be initiated by the Investigator if he/she determines it is in the best interest of the patient.

6.2.4 **Protocol Deviations**

All deviations from the requirements of this Clinical Investigation Plan will be considered protocol deviations.

A major protocol deviation is a protocol deviation that may affect the scientific soundness of the protocol or the rights, safety, or welfare of the patients. Major protocol deviations require urgent reporting to the Study Monitor and the Institutional Review Board/ Ethics Committee.

Patient-level deviations are those that occur in direct association with a specific study patient. These include, but are not limited to, deviations from informed consent procedures, inclusion/exclusion criteria, protocol-specified procedures and assessments, and device handling and usage.

Site-level deviations are those that occur at the study center but are not directly related to a study specific patient. All efforts should be made to avoid any protocol deviation.

6.3 Blinding

This is a single-blind study. The following individuals will be blinded to the subject's treatment allocation:

- Subject and his/her family members
- Site personnel administering neurological evaluations (NIHSS and mRS); these individuals will also be blinded to DW-MRI results
- Members of the Data Safety Monitoring Committee
- MRI Core Laboratory personnel performing imaging analysis

Un-blinding will occur only after the database has been locked for the analysis of the primary endpoint or to protect subject rights, welfare, or well-being at the request of the DSMB. The circumstances under which the DSMB may request unblinding to treatment allocation will be outlined in the DSMB charter prior to the onset of the trial.

If a site investigator determines it is necessary to reveal treatment allocation to the subject as a result of complication or injury, he or she is requested to notify the Sponsor.

7.0 Study Procedures

7.1 Study Schedule of Procedures and Assessments

Table 7. Study Schedule of Procedures and Assessments- **Phase I (TriGuard HDH)**

	Screening/ Baseline	Procedure (day 0)	Post-Procedure / Pre-Discharge	30-day Follow-up (30 ± 7 days)	90-day Follow-up (90 ± 14 days)
Written Informed Consent	X				
Medical History	X				
Physical Examination[1]	X		X	X	X
Review of Eligibility Criteria[2]	X	X			
Clinical Frailty Scale	X				X
12-lead ECG[3]	X		X		
Concomitant Medications	X	X	X	X	X
Pregnancy Test[4]	X				
Hematology/Chemistry[5]	X		X		
Cardiac Enzymes[6]	X		X		
CT Imaging[7]	X				
Cerebral DW-MRI[8]			X		
NIH Stroke Scale[9]	X		X	X	X
Modified Rankin Scale[9]	X		X	X	X
Neuropsychological test battery[10]	X		X	X	X
SF-36 Health Survey[11]	X			X	X
TAVI		X			
Echocardiography (SOC)[12]			X		
TriGuard HDH deployment		X			
Adverse Events		X	X	X	X

[1] Physical examination to include heart rate, blood pressure, and ischemic / anginal status (CCS or silent ischemia). The screening/baseline assessment must also include NYHA functional capacity, height, and weight.

[2] If the full screening/baseline review of eligibility criteria is conducted before the day of enrollment, the following repeat review of selected eligibility criteria should be performed on the day of enrollment and randomization (§6.2.1) to confirm study eligibility, using the most recent available laboratory values and clinical assessments: 1.) Ensure that the subject has not had symptoms or chemistry results indicating acute myocardial infarction (§6.1.2.1.5); 2.) Ensure that the most recent eGFR remains ≥30 (§6.1.2.1.10); 3.) Ensure that there are no signs of cardiogenic shock or severe hypotension (systolic blood pressure <90 mm Hg) (§6.1.2.1.13); and 4.) Review the planned approach for TAVI, as certain approaches will make the subject ineligible for the study (§6.1.2.1.1, §6.1.2.1.2)

[3] Screening/baseline ECG may be performed up to 30 days prior to procedure, as long as there have been no intervening signs or symptoms of myocardial ischemia (in which case the ECG should be performed within 24 hours prior to enrollment). The post-procedure ECG must be performed within 24 hours of the procedure or prior to hospital discharge (whichever occurs first).

[4] Female patients of childbearing potential must have a pregnancy test within 14 days prior to the procedure

[5] Hematology and chemistry within 14 days prior to the procedure are defined in §7.2.

[6] For the screening/baseline assessment, cardiac enzymes (CK), isoenzymes CK-MB or troponins obtained up to 14 days prior to the procedure (or on current admission) are acceptable, provided there has been no intervening episode of myocardial ischemia (in which case cardiac enzymes should be confirmed within 24 hours prior to enrollment). Post-procedure, CK/CKMB or troponin (preferably CKMB isoenzyme) will be measured at 12-24 hours post-procedure, at 24±3 hours after the first measurement, and again at 72±6 hours post-procedure or at discharge (whichever occurs first). If cardiac biomarkers are elevated, they should be repeated daily until values show a decline.

[7] Multi-slice CT angiography of the left heart, aorta, great vessels and peripheral access vessels performed up to 1 year prior to procedure should be submitted for review.
[8] DW-MRI must be performed 2 to 5 days (≥48 to <144 hours) post-procedure.
[9] The NIHSS and mRS (in addition to the neuropsychological test battery) must be performed 2 to 5 days (≥48 to <144 hours) post-procedure by a neurologist or a clinical designee (e.g. neurology fellow). A full neurological evaluation should be performed by a neurologist in all patients in whom a stroke or TIA is suspected on the basis of the NIHSS, mRS, or other signs or symptoms.
[10] A brief paper-and-pencil neuropsychological test battery (§16.7), will be administered up to 30 days prior to procedure, 2 to 5 days (≥48 to <144 hours) post-procedure, and at the 30- and 90-day clinic visits.
[11] The Short Form 36 Health Survey (SF-36) (§16.11) will be administered up to 30 days prior to procedure and at the 30- and 90-day clinic visits. When administered during a visit that includes other assessments, the SF-36 should be performed first.
[12] If echocardiography (transthoracic or transesophageal) was performed after TAVR prosthesis implantation as part of the standard of care, the relevant parameters (including mean aortic valve gradient, peak velocity, and degree of prosthetic aortic valve regurgitation) must be captured on the eCRF for evaluation in-hospital TAVI device success (§□).

Table 7a. Study Schedule of Procedures and Assessments- **Phase II (TriGUARD *3*)**

	Screening/ Baseline	Procedure (day 0)	Post-Procedure	30-day Follow-up (30 ± 7 days)	90-day Follow-up (90 ± 14 days)
Written Informed Consent	X				
Medical History	X				
Physical Examination[1]	X		X	X	
Review of Eligibility Criteria[2]	X	X			
Clinical Frailty Scale	X				
12-lead ECG[3]	X		X		
Concomitant Medications	X	X	X	X	
Pregnancy Test[4]	X				
Hematology/Chemistry[5]	X		X		
Cardiac Enzymes[6]	X[6]		X[6]		
CT Imaging[7]	X				
Cerebral DW-MRI[8]			X		
NIH Stroke Scale[9]	X		X	X	
Modified Rankin Scale[9]	X		X	X	
TAVI		X			
Echocardiography (SOC)[10]			X		
Device deployment		X			
Adverse Events		X	X	X	
Phone call to assess mortality/ Stroke					X

[1] Physical examination to include heart rate, blood pressure, and ischemic/anginal status (CCS or silent ischemia). The screening/baseline assessment must also include NYHA functional capacity, height, and weight.
[2] If the full screening/baseline review of eligibility criteria is conducted before the day of enrollment, the following repeat review of selected eligibility criteria should be performed on the day of enrollment and randomization (§6.2.1) to confirm study eligibility, using the most recent available laboratory values and clinical assessments: 1) Ensure that the subject has not had symptoms or chemistry results indicating acute myocardial infarction (§6.1.2.1.5); 2) Ensure that the most recent eGFR remains ≥30 (§6.1.2.1.10); 3) Ensure that there are no signs of cardiogenic shock (§6.1.2.1.13); and 4) Review the planned approach for TAVI, as certain approaches will make the subject ineligible for the study (§6.1.2.1.1)
[3] Screening/baseline ECG may be performed up to 30 days prior to procedure, as long as there have been no intervening signs or symptoms of myocardial ischemia (in which case the ECG should be performed within 24 hours prior to enrollment). The post-procedure ECG must be performed within 24 hours of the procedure or prior to hospital discharge (whichever occurs first).

[4] Female patients of childbearing potential must have a pregnancy test within 14 days prior to the procedure
[5] Hematology and chemistry within 14 days prior to the procedure are defined in §7.2.
[6] For the screening/baseline assessment, cardiac enzymes (CK), isoenzymes CK-MB or troponins obtained up to 14 days prior to the procedure (or on current admission) are acceptable, provided there has been no intervening episode of myocardial ischemia (in which case cardiac enzymes should be confirmed within 24 hours prior to enrollment). Post-procedure CK/CKMB or troponin (preferably CKMB isoenzyme) will be measured post procedure when clinically indicated. If cardiac biomarkers are elevated, they should be repeated per local standard of care.
[7] Multi-slice CT angiography of the left heart, aorta, great vessels and peripheral access vessels performed up to 1 year prior to procedure should be submitted for review.
[8] DW-MRI must be performed 2 to 5 days (≥48 to <144 hours) post-procedure.
[9] The NIHSS and mRS must be performed 2 to 5 days (≥48 to <144 hours) post-procedure by a neurologist or a clinical designee (e.g. neurology fellow). A full neurological evaluation should be performed by a neurologist in all patients in whom a stroke or TIA is suspected on the basis of the NIHSS, mRS, or other signs or symptoms.
[10] If echocardiography (transthoracic or transesophageal) was performed after TAVI prosthesis implantation as part of the standard of care, the relevant parameters (including mean aortic valve gradient, peak velocity, and degree of prosthetic aortic valve regurgitation) must be captured on the eCRF for evaluation in-hospital TAVI device success.

7.2 Screening / Baseline

The following tests and examinations must be performed prior to the procedure to verify eligibility and to collect baseline study data:

- Relevant medical history and patient demographic information, including STS Risk Score and EuroSCORE II risk evaluations
- Physical examination including ischemic / anginal status (CCS or silent ischemia), NYHA functional capacity, heart rate, blood pressure, height, and weight
- Frailty assessment with the Clinical Frailty Scale
- Concomitant medication documentation
- Review of the study eligibility criteria (inclusion and exclusion). NOTE: If the full screening/baseline review of eligibility criteria is conducted before the day of enrollment, the following repeat review of selected eligibility criteria should be performed on the day of enrollment and randomization (§6.2.1) to confirm study eligibility, using the most recent available laboratory values and clinical assessments:
    - Ensure that the subject has not had symptoms or chemistry results indicating acute myocardial infarction (§6.1.2.1.5)
    - Ensure that the most recent eGFR remains ≥30 (§6.1.2.1.10)
    - Ensure that there are no signs of cardiogenic shock (§6.1.2.1.13)
    - Review the planned approach for TAVI, as certain approaches will make the subject ineligible for the study (§6.1.2.1.1, §6.1.2.1.2)
- Routine laboratory tests including:
    - Hematology - hemoglobin, hematocrit, platelet count, white blood cell count within 14 days prior to the procedure

  - Chemistry - creatinine, ALT/serum glutamic-pyruvic transaminase (SGPT), and AST/serum glutamic-oxaloacetic acid transaminase (SGOT) within 14 days prior to the procedure,
  - Cardiac enzymes (CK), isoenzymes CK-MB or troponins should be obtained when clinically indicated (for example if there is a suspected ischemic event).
  - Female patients of childbearing potential must also have a pregnancy test within 14 days prior to the procedure.
- At the investigator's discretion and according to site standard practice, subjects requiring warfarin therapy may undergo a pre-procedure Coagulation Panel including prothrombin time, partial thromboplastin time (PTT) and International Normalized Ratio (INR) to ensure compliance with the concomitant therapy recommendations (§7.3).
- A 12-lead electrocardiogram. An ECG performed within 30 days prior to the procedure may be used as the baseline ECG provided there have been no signs or symptoms of myocardial ischemia between the time of the ECG and enrollment (in which case the ECG should be performed within 24 hours prior to enrollment).
- CT imaging (standard and contrast-enhanced angiography preferred) of the left heart, aorta, great vessels, and peripheral access vessels performed up to 1 year prior to the procedure should be submitted for review.
- NIH Stroke Scale (NIHSS) up to 14 days prior to procedure. Neurologic status evaluation using the NIH stroke scale shall also be performed 2-5 days post-procedure and during each follow-up assessment. The examination must be performed by a neurologist, or a clinical designee (e.g. neurology fellow).
- Modified Rankin Scale (mRS) up to 14 days prior to procedure. The mRS will also be performed 2-5 days post-procedure and during each follow-up assessment. The assessment must be performed by a neurologist or a clinical designee (e.g. neurology fellow).
- A full neurological evaluation should be performed by a neurologist in all patients in whom a stroke or TIA is suspected on the basis of the NIHSS, mRS, or other signs or symptoms.
- A neuropsychological test battery (§16.7) will be administered up to 30 days prior to procedure by a qualified individual, and will be re-administered 2-5 days post-procedure and at 30 and 90 days. The test battery includes: (Phase I only)
  - Montreal Cognitive Assessment (MoCA) - A cognitive screening instrument that includes tasks that assess attention and concentration, executive functions, memory, language, visuoconstructional abilities, abstraction, calculations, and orientation. It takes approximately 10 minutes to administer and is available in several languages.
  - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) - A comprehensive, but brief, neuropsychological battery that includes assessment of immediate memory, visuospatial/constructional abilities, language, attention, and delayed memory. The RBANS is available in many different languages and typically takes less than 30 minutes to administer. Alternate forms of the tests are used for repeat testing.

- Trail Making Test Parts A & B. These tests evaluate attention, psychomotor speed, and mental flexibility. In Part A, the subject connects 25 encircled numbers in ascending order as quickly as possible. In Part B, the subject connects encircled numbers and letters in ascending order, alternating between the two (i.e., 1-A-2-B-etc.). The total administration time is less than 10 minutes.

- The Short Form 36 Health Survey (SF-36v2) will be administered up to 30 days prior to procedure, and will be re-administered at 30. The SF-36 is a 36-item questionnaire that measures health-related quality of life across 8 physical and mental domains. It is available in many different languages and takes approximately 10 minutes to administer. When administered during a visit that includes other assessments, the SF-36 should be performed first (Phase I only).

7.3 Concomitant Therapies

Selection and dosing of procedural and post-procedural concomitant therapies, including antiplatelet and anticoagulant therapies, will be performed according to physician standard practice, in accordance with local standards of care and published guidelines. Each site is encouraged to commit to a consistent antiplatelet regimen to be applied to all subjects enrolled in the trial, independent of treatment group.

The investigators recommend (but do not require) that all subjects receive the medication regimen listed below (Table 8). All medications administered should be recorded in the patient's medical record and the CRF.

Table 8: Concomitant Medications

Timing	Medication	Recommended Doses
Prior to Procedure	IV Heparin or low molecular weight heparin or bivalirudin	Per routine hospital practice
During Procedure	IV Heparin or low molecular weight heparin or bivalirudin	Per routine hospital practice. It is recommended to maintain an ACT > 250 seconds.†
Post Procedure*	Acetylsalicylic acid (ASA)	75-100 mg QD indefinitely
	Clopidogrel	75 mg QD for a minimum of 6 months or longer based on local guidelines.

†Peak and nadir intraprocedural ACT measurements must be recorded in the CRF for all subjects.

Note for patients receiving warfarin therapy:

- *If the patient is on warfarin therapy prior to the procedure, the following is recommended:*
  - *Discontinue warfarin three days prior to the procedure*
  - *Confirm that the INR is <1.8 prior to the procedure*
  - *ASA 75-100 mg or clopidogrel 75 mg for 3 days prior to the procedure*
- *If the patient is on warfarin therapy post-procedure, it is recommended that the patient is prescribed either daily aspirin (75-100 mg) or daily clopidogrel (75 mg).*

  Minimum recommended maintenance dosages can be higher based on physician's discretion.

7.4 TAVI Procedure

TAVI will be performed according to standard institutional practice under local or general anesthesia and via the transfemoral approach at the discretion of the investigator.

In subjects in the Intervention or Roll-in Groups, the TriGuard HDH or TriGUARD *3* device will be advanced and deployed across the aortic arch to cover the ostia of the 3 major vessel takeoffs (innominate, left carotid and subclavian arteries) at the initiation of the TAVI procedure and withdrawn at the completion of the procedure. Please refer to the TriGuard HDH or TriGUARD *3* Instructions For Use for additional information.

Device coverage and positioning must be verified by fluoroscopy (a steep left anterior oblique [LAO] view is recommended), with particular attention paid to 1.) Device coverage after initial deployment, 2.) Device positioning after final deployment of the first prosthetic valve, and 3.) Device positioning after the procedure is complete (i.e., after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed). All imaging should be forwarded to the Angiographic Core Laboratory for analysis. For additional details, please refer to the Angiographic Imaging Acquisition Guidelines (§16.8).

7.5 Post-procedure Follow-up

The procedure is considered complete once the last guiding catheter has been removed from the patient and the patient is off the table. Thereafter, if a guiding catheter is re-introduced, this is considered a repeat intervention, which must be documented.

The post-procedure follow up will consist of:

- Physical examination including ischemic / anginal status (CCS or silent ischemia), heart rate, and blood pressure
- Documentation of any adverse events/ serious adverse events occurring since the point of enrollment
- Current concomitant medications documentation, including antiplatelet and anticoagulant therapy
- Routine laboratory tests including:
    - Hematology - hemoglobin, hematocrit, platelet count, white blood cell count
    - Chemistry - creatinine. Serum creatinine should be measured within 48 hours post-procedure in all subjects. Subjects with elevated serum creatinine (≥1.5x baseline OR >0.3 mg/dL [>26.4 mmol/L]) should have continued assessments to 7 days post-procedure or until discharge (whichever occurs first) to assess acute kidney injury.
    - Cardiac enzymes: CK/CKMB or Troponin (preferably CKMB isoenzyme) will be measured when clinically indicated. If cardiac biomarkers are elevated, they should be repeated per local standard of care.
- A 12-lead ECG, to be completed within 24 hours post-procedure or prior to hospital discharge (whichever occurs first)
- If echocardiography (transthoracic or transesophageal) was performed after TAVR prosthesis implantation as part of the standard of care, the relevant parameters (including mean aortic valve gradient, peak velocity, and degree of prosthetic aortic

valve regurgitation) must be captured on the eCRF for evaluation in-hospital TAVI device success (§□)

- Diffusion-weighted MRI of the brain 2 to 5 days (≥48 to <144 hours) post-procedure
- NIH Stroke Scale (NIHSS). Neurologic status evaluation using the NIH stroke scale shall be performed 2 to 5 days (≥48 to <144 hours) post-procedure and during each follow-up assessment. The examination must be performed by a neurologist or a clinical designee (e.g. neurology fellow).
- Modified Rankin Scale (mRS) shall be performed 2 to 5 days (≥48 to <144 hours) post-procedure and during each follow-up assessment. The assessment must be performed by a neurologist or a clinical designee (e.g. neurology fellow).
- A full neurological evaluation should be performed by a neurologist in all patients in whom a stroke or TIA is suspected on the basis of the NIHSS, mRS, or other signs or symptoms.
- A neuropsychological test battery (§16.7) will be administered 2 to 5 days (≥48 to <144 hours) post-procedure by a qualified individual. The test battery includes: (Phase I only).
    - Montreal Cognitive Assessment (MoCA)
    - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
    - Trail Making Test Parts A and B

Prior to hospital discharge, research staff should also review the follow-up requirements with the subject to help ensure that the patient returns to the clinic for the one-month follow-up visit. Telephone numbers should be obtained from the patient to ensure the ability to contact him or her at the required time. These phone numbers should include all home numbers, work numbers and primary physician numbers. A phone number of a relative or friend should also be requested.

Note: All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. Any clinically-indicated neuroimaging should be forwarded to the MRI Core Laboratory.

7.6 One-month Follow-up (Clinic Visit)

All subjects will return to the clinic at 30 days (± 7 days) post-procedure for a clinical evaluation.

The 30 day follow-up visit will consist of the following assessments:

- Physical examination
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation
- Current concomitant medication documentation, including antiplatelet and anticoagulant therapy
- NIH Stroke Scale (NIHSS): Neurologic status evaluation using the NIH stroke scale must be performed by a neurologist or a clinical designee (e.g. neurology fellow).
- Modified Rankin Scale (mRS) must be performed by a neurologist or a clinical designee (e.g. neurology fellow).

- A full neurological evaluation should be performed by a neurologist in all patients in whom a stroke or TIA is suspected on the basis of the NIHSS, mRS, or other signs or symptoms.
- A neuropsychological test battery (§16.7), to be administered by a qualified individual. The test battery includes: (Phase I only)
    - Montreal Cognitive Assessment (MoCA)
    - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
    - Trail Making Test Parts A and B
- The Short Form 36 Health Survey (SF-36) (Phase I only)

Prior to concluding the visit, research staff should also review the follow-up requirements with the subject to help ensure that the patient can be contacted by telephone at the three-month follow-up time point.

Note: All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. Any clinically-indicated neuroimaging should be forwarded to the MRI Core Laboratory.

7.7 Three-month Follow-up

7.7.1 **Phase I:**

All subjects in Phase I were expected to return to the clinic at 90 days (± 14 days) post-procedure for a clinical evaluation.

The 90 day follow-up visit consisted of the following assessments:

- Physical examination including ischemic / anginal status (CCS or silent ischemia), heart rate, and blood pressure
- Frailty assessment with the Clinical Frailty Scale
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation
- Current concomitant medication documentation, including antiplatelet and anticoagulant therapy
- NIH Stroke Scale (NIHSS): Neurologic status evaluation using the NIH stroke scale must be performed by a neurologist or a clinical designee (e.g. neurology fellow).
- Modified Rankin Scale (mRS) must be performed by a neurologist or a clinical designee (e.g. neurology fellow).
- A full neurological evaluation should be performed by a neurologist in all patients in whom a stroke or TIA is suspected on the basis of the NIHSS, mRS, or other signs or symptoms.
- A neuropsychological test battery (§16.7), to be administered by a qualified individual. The test battery includes:
    - Montreal Cognitive Assessment (MoCA)
    - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
    - Trail Making Test Parts A and B

- The Short Form 36 Health Survey (SF-36)

Note: All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms. Any clinically-indicated neuroimaging should be forwarded to the MRI Core Laboratory.

7.7.2 **Phase II:**

In Phase II, a telephone contact at 90 days (± 14 days) post-procedure will establish:

- Mortality
- Stroke

If death or stroke is reported, source documentation will be requested from treating facility to enable CEC adjudication of cause of death (cardiovascular [subclassified and neurologic-event related] or non-cardiovascular) and stroke classification according to the protocol-specified definitions.

8.0 Device Accountability

The Site Principal Investigator is responsible for device accountability at his/her trial site and must maintain associated trial records according to 21 CFR Part 812.140 (§15.5.2). The investigator may assign the responsibility for device accountability to an appropriate study staff member, but remains the final responsible person.

The investigator will maintain device use/disposition records that document device delivery to the trial site, the inventory at the site, administration to each patient as well as any device that was opened but not used. These records must include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial patients. The investigator must maintain records that adequately document which device was used (or exposed to the circulation) of each subject and any device malfunctions.

At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator's copy of the device reconciliation records must document all device usage (including devices that were opened but not used) and any unused devices that have been returned to the sponsor.

9.0 Adverse Events, Serious Adverse Events, and End-points Potentially Meeting End-point Criteria

In this study, patients should be encouraged to report adverse events (AEs) spontaneously or in response to general, non-directed questioning. Any time during the study, the patient may volunteer information that resembles an adverse event (AE). If it is determined that a clinically significant AE has occurred, the investigator should obtain all the information required to complete the AE CRFs. Non-clinically-significant adverse events will not be required post discharge from the initial study procedure.

9.1 Adverse Events (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study device.

NOTE: This definition includes events related to the study device or to the procedures involved, but does not imply that there is a relationship between the adverse event and the study device.

Pre-Existing Conditions:

Pre-existing medical conditions or a repeat of symptoms reported prior to the TAVR procedure will not be recorded as an AE. Pre-existing conditions that worsen during a study are to be considered adverse events. For users or other persons, this classification is restricted to events related to the study device.

9.2 Serious Adverse Events (SAE)

A serious adverse event is an adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolongation of existing hospitalization
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function.
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

9.3 Adverse Device Effect (ADE)

An adverse device effect is an adverse event related to the use of a medical device. This includes:

- Any adverse event resulting from insufficiencies or inadequacies in the Instructions for Use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device
- Any event that is a result of a use error or intentional misuse

9.4 Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

9.5 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).

9.6 Device Deficiencies, Malfunctions, and Use Error

Investigators are instructed to report all possible device deficiencies, malfunctions, misuse or use error observed during the course of the trial. These incidents will be documented in the case report form provided as follows:

- **Device deficiency**: Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.
- **Device malfunction**: Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol. NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use, but does not perform as described in the Instructions for Use.
- **Use error:** Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
- **Device misuse:** Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.

9.7 End-points Potentially Meeting End-point Criteria

Investigators are instructed to report all cardiovascular events and all adverse events potentially meeting end-point criteria. These events will be documented in the case report form as SAEs and be assessed by the medical monitor. Events classified as potential end-points will then be sent to CEC adjudication (§11.2).

9.8 Documentation

Adverse events must be listed on the appropriate CRF. All AEs will be characterized by the following criteria:

- Intensity or Severity
- Relatedness
- Outcome
- Treatment or Action Taken

9.8.1 **Intensity or Severity**

The following categories of the intensity of an adverse event are to be used:

Mild	Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes with the patient's usual activity and/or requires symptomatic treatment.
Severe	Symptom(s) causing severe discomfort and significant impact of the patient's usual activity and requires treatment.

9.8.2 **Relatedness**

The investigator will use the following definitions to assess the relationship to the device:

Not related	The cause of the AE is known and the event is not related to any aspect of study participation.
Unlikely to be related	There is little or no temporal relationship to the study device and/or a more likely alternative etiology exists.
Possibly related	There is a reasonable possibility that the event may have been caused by study participation. The AE has a **timely relationship** to the study procedure(s); **however, follows no known pattern of response**, and an alternative cause seems more likely or there is significant uncertainty about the cause of the event.
Probably related	It is likely that the event was caused by study participation. The AE has a **timely relationship** to the study procedure(s) and **follows a known pattern of response**; a potential alternative cause, however, may explain the event.
Related	A **related** event has a **strong temporal relationship** and an alternative cause is unlikely.

If the relationship between any adverse event and the use of the investigational medical device is considered to be possibly or probably related, that event will be classified as an ADE or SADE.

9.8.3 **Outcome**

The clinical outcome of the AE or SAE will be characterized as follows:

Death	The SAE CRF must be completed for this outcome
Recovered without sequelae	The patient returned to baseline status
Ongoing	Patient did not recover and symptoms continue;
Recovered with sequelae	The patient has recovered but with clinical sequelae from the event
Unknown	The patient outcome is unknown

9.8.4 **Treatment or Action Taken**

The treatment or action taken after the occurrence of an AE or SAE will be reported as:

Interventional Treatment	Surgical, percutaneous or other procedure
Medical Treatment	Medication dose reduction/interruption or discontinuation, or medication initiated for event
None	No action is taken

9.9 Reporting

9.9.1 **General Adverse Event Reporting Procedures**

Investigators are required to keep records on "all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)" according to 21 CFR 812.140. Adverse event collection will occur from the point of study enrollment to study closure. All new or worsening (from baseline) clinically significant adverse events will be captured on the AE CRF through the 90-day follow-up telephone visit. Non-clinically-significant adverse events will not be required post discharge from the initial study procedure. It is the responsibility of the Investigator to assess the subject for adverse events and, if it is determined that a clinically significant AE has occurred, to capture the required adverse event information on the AE CRF. Independent monitoring will be conducted (§14.1) to review source documentation and verify the complete and accurate capturing of adverse events.

The general procedure for investigators reporting any adverse event is as follows:

- If an adverse event occurs, complete all sections of the Adverse Event CRF
- Each unique event/diagnosis must be documented separately
- Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition
- The AE CRF must be reviewed by the investigator

For adverse events not meeting the criteria for an SAE or (potential) UADE, the sponsor recommends that the Investigator notify the sponsor within 10 working days of first learning of the AE using the electronic data capture (EDC) CRF. If necessary, the Investigator may be requested to provide de-identified copies of source documentation (e.g., physician/nurse notes or summaries) regarding the event.

The Investigator must also notify the responsible IRB/EC regarding new and significant safety information and any events identified by Keystone Heart Ltd. that require expedited FDA or other regulatory authority reporting as serious, unexpected, and related to the investigational device. It is the responsibility of the investigator to ensure site-specific IRB/EC reporting requirement are met.

The sponsor is responsible for reporting SAEs and device deficiencies to regulatory authorities in line with applicable regulatory requirements and for reviewing the risk analysis, determining the need for corrective or preventative action, and informing investigators and regulatory authorities accordingly.

9.9.2 **Serious Adverse Events**

Keystone Heart Ltd. recommends that the Investigator notify the sponsor within 3 working days of first learning of any SAE using the EDC CRF. All cardiovascular events and all adverse events potentially meeting endpoint criteria will be considered an SAE (even if they do not result in death or prolong the hospitalization) and should be reported as well (see also section 11.2). If necessary, the Investigator may be requested to provide copies of de-

identified source documentation (e.g., physician/nurse notes or summaries) regarding the event. The sponsor will conduct an evaluation of the event and, if it is determined by the sponsor to be a UADE, it will be reported as described in the following section.

At EU sites (phase I), Serious Adverse Device Effects (SADEs) must be reported to genae, N.V. within 48 hours of knowledge if required by local or national regulations. Contact details are as follows:

genae, N.V.
Justitiestraat 6B
2018 Antwerp, Belgium
Tel: +32 3 290 0306
Fax: +32 3 290 0307

It is the responsibility of each Investigator to report all serious adverse events and/or serious adverse device effects and device deficiencies that could have led to a serious adverse device effect to the IRB/EC, according to national regulations and IRB/EC requirements. If required by national regulations, the Investigator may also be required to report SAEs to the regulatory authority.

European investigators (phase I) who become aware of an event must report the event to **genae** and to the **Sponsor**. While there is no legal requirement within the Medical Device Directives obliging users to have an active role in the medical devices vigilance system, user involvement is critical to successful post market surveillance by 1.) Ensuring that suspected incidents are communicated to manufacturers, and 2.) Making the proper implementation of field safety corrective actions possible.

9.9.3 **Unanticipated Adverse Device Effects**

Investigators must report any (potential) unanticipated adverse device effects to the sponsor and their IRB as soon as possible but no later than within 5 working days after the investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately via telephone (contact details follow) as well as on the eCRF.

Sponsor contact (US):
M. Pauliina Margolis, MD, PhD
Chief Medical Officer
Tel: 305.972.8447
email: pauliina.margolis@keystoneheart.com

Sponsor contact (OUS):
Ron Nitzan, PhD
Vice President, Regulatory and Quality Affairs
Tel: +972 4 615 8005
Fax: +972 4 615 8099
email: ron.nitzan@keystoneheart.com

Investigators should consider the device labeling and the listing of expected adverse events (§9.10) in determining whether an event may qualify as “unanticipated.”

If an event is determined by Keystone Heart Ltd. to be a UADE, the sponsor will report the event to the FDA, relevant competent authorities and the European Databank on Medical Devices (Eudamed) if necessary (in accordance with MEDDEV 2.12-1), and to all investigators to enable reporting to their respective IRB/EC. The sponsor will provide this notification within 10 days after first receiving notice of the effect [21 CFR 812.150].

If the sponsor and the DSMB determine that the event presents an unreasonable risk to the participating subjects, the sponsor must terminate all investigations or parts of investigations presenting the risk in the clinical trial not more than 5 working days after making that determination, and not more than 15 working days after the sponsor first received notice of the effect [21 CFR 812.26]. Follow-up visits for enrolled subjects will continue according to the schedule of assessments.

9.10 Expected Adverse Events

As with any endovascular intervention, TAVI involves some risks and possible complications. The following anticipated events have been identified as possible complications of TAVI procedures:

- Acute cardiovascular surgery (need for)
- Acute coronary artery occlusion
- Acute myocardial infarction
- Acute neurological events such as stroke, transient ischemic attack (TIA), and encephalopathy
- Allergic reaction to contrast, antiplatelet therapy or device component materials
- Angina pectoris
- Anesthesia reactions
- Aneurysm or pseudoaneurysm
- Arteriovenous fistula
- Ascending or descending aorta trauma
- Atrial or ventricular arrhythmias or fibrillation or sustained heart palpitations requiring therapy
- Bleeding complications such as hematoma and hemorrhage
- Blood loss requiring transfusion
- Bowel ischemia
- Coronary artery or other vascular injury, dissection, or perforation (which may require repair)
- Embolism (air, tissue, device, or thrombus)
- Fever
- Femoral nerve damage
- Hemodynamic changes
- Hypertension or hypotension (sustained requiring therapy)
- Infection, including endocarditis and septicemia
- Pain (at the femoral puncture site, abdominal, back, or other)
- Percutaneous coronary intervention (need for)
- Peripheral ischemia, peripheral nerve damage

- Pulmonary edema
- Pyrogenic reaction
- Renal complications, injury, or failure
- Unstable angina
- Vascular complications which may require vessel repair
- Vessel spasm (sustained, not responding to therapy)

In addition to the risks listed above, the potential risks specifically associated with the TriGuard HDH or TriGUARD *3* procedure include, but may not be limited to, the following:

- Dissection of the innominate artery by improper manipulations, disruption or migration of the TriGuard HDH CEPD filter due to passage of other instrumentation, e.g.: balloon, stent, catheter, wire
- Blue toe syndrome or blue discoloration of a toe
- Femoral bleeding at the access site
- Local trauma to the aortic wall due to device migration

10.0 Risk/Benefit Analysis

10.1 Potential Risks and Discomforts

Enrollment in the trial involves exposure to some risks. Most risks of trial participation are not materially different than those encountered by an individual undergoing TAVI outside the context of the trial (§9.10). However, the use of the TriGuard HDH or TriGUARD *3* embolic protection devices may involve exposure to additional risks (§9.10) as well as other potential risks of an unknown nature.

10.2 Methods to Minimize Risks

The clinical investigation plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators, adherence to pre-determined time points to assess subject clinical status, and regular clinical monitoring visits by Sponsor-appointment monitoring personnel. A dedicated contract research organization has been included in the study team to ensure high quality follow-up and minimize potential drop out. In addition, an independent Data Safety Monitoring Committee will monitor the safety of subjects throughout the trial.

10.3 Potential Benefits

The targeted trial population (subjects with severe symptomatic AS meeting indications for TAVI) has been demonstrated to be at risk for stroke and other neurological complications during and after the procedure. The study intervention has the potential to benefit subjects by preventing or reducing cerebral embolization during the TAVI procedure, limiting subsequent cerebral ischemia. Potential risks and benefits will be evaluated on an individual basis and discussed with each patient prior to enrollment in the study.

11.0 Study Committees

11.1 Patient Review Committee (PRC)

The PRC will ensure appropriate and consistent application of selected anatomic eligibility criteria to all potentially eligible subjects at all study sites. The PRC will consist of at least one imaging specialist, two interventional cardiologists, and a Sponsor representative (non-voting role).

Following initial pre-screening for study eligibility by the research team and documentation of informed consent, the following information will be submitted to the PRC for review for each potentially eligible subject:

- A completed Screening Worksheet
- The results of independent core laboratory analysis of CT imaging (standard and contrast-enhanced angiography preferred) of the left heart, aorta, great vessels, and peripheral access vessels performed up to 1 year prior to procedure.

The PRC will meet regularly during the enrollment phase to determine whether potential candidates meet selected applicable anatomic eligibility criteria (§6.1.2.1.15, §6.1.2.1.16, §6.1.2.1.17, §6.1.2.1.18, §6.1.2.1.19). PRC responsibilities, membership, meeting frequencies, and procedures will be outlined in the PRC charter prior to the onset of the trial.

11.2 Clinical Events Committee (CEC)

The CEC will be responsible for adjudicating all site-reported cardiovascular events and all adverse events potentially meeting endpoint criteria, in an ongoing fashion during the trial. In order to fully capture all endpoints, events potentially meeting end-point criteria will be considered an SAE (even if they do not result in death or prolong the hospitalization) and sent to the medical monitor for further assessment. Events appropriately classified as potential endpoints by the medical monitor will be sent to CEC for adjudication.

Events potentially meeting end-point criteria and therefore defined as SAE for this purpose include:

- Death
- Stroke/TIA or any other Neurological Dysfunction (NeuroARC definitions)
- MI or Coronary artery obstruction requiring intervention
- Bleeding (including life-threatening or disabling bleeding, Major and Minor bleeding)
- Acute kidney injury (stage 2 or 3 or requiring dialysis)
- Major vascular complications
- Valve-related dysfunction requiring repeat procedure

The CEC will include at least one interventional cardiologist with relevant clinical experience and one neurologist with experience in clinical trials involving stroke who are otherwise independent of the Sponsor or the conduct of the study. Members will not have scientific, financial or other conflicts of interest related to Keystone Heart Ltd. or the Investigators. The CEC will operate and conduct all meetings and event reviews independent of the Sponsor unless specific expert knowledge regarding the characteristics or function of the study device is requested by the CEC from the Sponsor.

The CEC will meet regularly throughout the study to adjudicate events in an ongoing and timely fashion. The adjudication process, event definitions and required source document materials for each types of event will be pre-specified in the CEC Charter prior to the onset of the trial. The adjudication process will include CEC member review of copies of all relevant medical records and imaging studies associated with an event reporting. All adjudication decisions will be made by the CEC in an independent fashion based upon review of all available medical evidence associated with an event.

11.3 Data and Safety Monitoring Board (DSMB)

The Data Safety Monitoring Committee (DSMB) is responsible for the oversight and safety monitoring of the study. The DSMB advises the Sponsor regarding the continuing safety of the trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. The DSMB will be composed of members are leading experts in cardiovascular medicine, vascular neurology (with experience in clinical trials involving stroke), and biostatistics who are not participating in the trial and have no affiliation with the sponsor.

During the enrollment phase of the trial, the DSMB will review accumulating safety data to monitor for the incidence of serious adverse events that would warrant modification or termination of the trial according to a pre-specified safety monitoring plan. Any DSMB recommendations for study modification or termination prompted by concerns regarding subject safety or issues relating to data monitoring or quality control will be submitted in writing to the Sponsor for consideration and final decision. However, if the DSMB at any time determines that a potential serious risk exists to subjects in this trial, the DSMB chairman will immediately notify the Sponsor.

The DSMB will meet at regular intervals to review the safety data. DSMB responsibilities, membership, meeting frequencies, and procedures will be outlined in the DSMB charter prior to the onset of the trial. The circumstances under which the DSMB may request unblinding to treatment allocation will also be outlined in the charter.

12.0 Statistical Considerations and Analysis Plan

12.1 General Analysis Definitions

Analysis will be conducted using SAS (version 9.3 or greater), unless otherwise noted. Descriptive statistics for continuous variables will include mean, median, standard deviation, quartiles, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group. For time-to-event data, Kaplan-Meier estimates at the indicated time points will be displayed graphically. Further clarifications regarding endpoint criteria assessment and analysis between subjects will be provided in the Statistical Analysis Plan (SAP).

12.1.1 **Adaptive Design**

Once at least 50% of the initial randomized Phase II cohort has been enrolled and has reached the 30 day primary efficacy endpoint evaluation time point, the independent unblinded statistician will perform a conditional power analysis. If the trial, based on the results at that point is either ≤40% powered to achieve success in meeting the primary efficacy endpoint or is ≥80% powered to achieve the primary efficacy endpoint no sample size reestimation will be required. If the conditional power of the study is >40% but <80% the independent unblinded statistician will recommend a sample size reestimation, subject to approval by the Sponsor. If this analysis determines that more than 225 randomized subjects

will be required to ensure adequate study power, enrollment may continue until the required number of subjects have been enrolled, or until the total subject limit for the study has been reached (whichever occurs first).

Promising zone computation

After the trial has enrolled 50% of the originally planned sample size of the initial randomized cohort (112 patients), an independent statistician will estimate all 4 levels of the Finkelstein-Schoenfeld hierarchy for device and control, and use these estimates to re-calculate the trial's power given the originally planned 225 Phase II patients.

If the trial power is between >40% and <80%, the trial will be considered promising and the trial will readjust the sample size to attain 80% power. If on the other hand the power falls to ≤ 40% or ≥ 80%, the sample size will not be adjusted.

Conditional power computation

The conditional power will estimate all four Finkelstein-Schoenfeld levels and use these estimates to simulate future enrolled patients. The power simulation will follow exactly the same algorithm as used to power the original Phase II study with updated estimates of effect size.

Alpha spending and controlling type I error

Since the study leadership and sponsor do not conduct any formal statistical hypothesis test, this design will not incur any alpha penalty or affect the overall type I error. As detailed by Mehta and Pocock[11] and based on the work of Chen[10] as long as the sample size reestimation occurs only when the conditional power falls in the promising zone, no additional alpha spend is required and the overall type I error is preserved.

12.2 Sample Size Calculation

12.2.1 **Hypotheses**

12.2.1.1.1 Primary Safety Hypothesis (Phase I and Phase II reported individually)

The primary safety hypothesis is that the rate of the primary safety endpoint (a composite of death, stroke, life-threatening of disabling bleeding, AKI [Stage 2 OR 3], coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure) in the group undergoing TAVI with either protection device system (Intervention Groups) at 30 days will be less in each device group (TriGuard HDH and TriGUARD *3*) compared separately to a performance goal (PG) of 34.4%.

Specifically, the primary safety analysis will assess if the Intervention group's safety event rate is significantly less than the PG of 34.4% using a one-sample z-test of proportions. The formal null and alternative hypotheses to be tested are:

$$H_0: \pi \geq 0.344$$

$$H_1: \pi < 0.344$$

where π is the true safety event rate for the Intervention arm.

The primary hypothesis test will be carried out by comparing the upper bound of the one-sided 95% confidence interval of the primary safety endpoint event rate in the intervention arm to the PG. With the planned evaluable sample size of 179 subjects and a one-sided alpha of 0.05, the critical value for rejection of the null hypothesis is 28.5%: if the primary

safety endpoint occurs in 28.5% or less of intervention group subjects, the performance goal will be met.

After accounting for a potential 5% loss to clinical follow-up at 30 days (including subjects who do not meet As Treated population criteria), the total required intervention group sample size is 190 subjects in each Phase. For Phase II 150 subjects randomized to the TriGUARD *3* and the 40-50 roll-ins will constitute the primary safety population.

Trial success depends on both primary endpoints being met in their primary analysis populations; i.e., the primary safety endpoint must be met in the primary (AT) population and the primary efficacy endpoint must be met in the primary (eITT) population in order for the trial to be declared a success. Because both primary endpoints (safety and efficacy) must be met (i.e., both H_0 must be rejected) for the trial to be declared a success, no adjustment to alpha for multiple endpoints is required for the two primary study endpoints.

12.2.1.1.2 Primary Efficacy Hypothesis

The primary hypothesis is that TAVI with the TriGUARD *3* system is superior to standard (unprotected) TAVI for the primary hierarchical composite efficacy endpoint of all-cause mortality or any stroke at 30 days (Tier 1), NIHSS worsening from baseline assessed at 2-5 days post-procedure (Tier 2), freedom from any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure (Tier 3), and total volume of post-procedure cerebral ischemic lesions detected by DW-MRI (Tier 4).

Specifically, the primary efficacy hypotheses are:

> H_0: The hierarchical composite of death/stroke, NIHSS worsening, freedom from any lesions detected by DW-MRI, and larger total lesion volumes is not different between Intervention and Control groups
>
> H_1: The hierarchical composite of death/stroke, NIHSS worsening, freedom from any lesions detected by DW-MRI, and larger total lesion volumes is lower in the Intervention group than in the Control group

The null hypothesis will be tested at the final analysis at a one-sided 0.025 level of significance. The null hypothesis will be tested using the chi-square test according to the method described in Finkelstein-Schoenfeld[2] and Pocock[77].

12.2.1.1.3 Hypothesis-driven Secondary Endpoints

In order to control alpha at 0.025 level overall, the secondary endpoints will be tested if and only if the primary study endpoints are met. Secondary testing will be conducted sequentially beginning with all stroke, followed by NIHSS worsening, followed by the composite of all-cause mortality and all stroke, followed by CNS Infarction, followed by total volume of cerebral ischemic lesions.

- **All stroke** [evaluated at 7 days in the eITT analysis population]

The hypothesis is that the event rate for all stroke in the Intervention Group at 7 days will be lower than the Control Group at 7 days.

The formal null and alternative hypotheses to be tested are:

H_0: $\pi_{STRK\text{-}I} = \pi_{STRK\text{-}C}$

H_1: $\pi_{STRK\text{-}I} < \pi_{STRK\text{-}C}$

where π_{STRK-I} is the true rate of all stroke in the Intervention arm and π_{STRK-C} is the true rate of all stroke in the Control arm.

The null hypothesis will be tested at a one-sided 0.025 level of significance using a two-sample z-test of proportions.

- **NIHSS worsening**, defined as an NIHSS score increase from baseline [evaluated at 2-5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

The hypothesis is that the rate of the patients with worsening NIHSS score in the Intervention Group at post-procedure (2-5 days post-procedure) will be lower than the Control Group at post-procedure (2-5 days post-procedure).

The formal null and alternative hypotheses to be tested are:

H_0: $\pi_{NIHSS-I} = \pi_{NIHSS-C}$

H_1: $\pi_{NIHSS-I} < \pi_{NIHSS-C}$

where $\pi_{NIHSS-I}$ is the true rate of worsening NIHSS scores in the Intervention arm and $\pi_{NIHSS-C}$ is the true rate of worsening NIHSS scores in the Control arm.

The null hypothesis will be tested at a one-sided 0.025 level of significance using a two-sample z-test of proportions.

- **Composite of all-cause mortality and all stroke** [evaluated at 7 days in the eITT analysis population]

The hypothesis is that the event rate for the composite of all-cause mortality and all stroke in the Intervention Group at 7 days will be lower than the Control Group at 7 days.

The formal null and alternative hypotheses to be tested are:

H_0: $\pi_{COMP-I} = \pi_{COMP-C}$

H_1: $\pi_{COMP-I} < \pi_{COMP-C}$

where π_{COMP-I} is the true rate of the composite of all-cause death and all stroke in the Intervention arm and π_{COMP-C} is the true rate of the composite of all-cause death and all stroke in the Control arm.

The null hypothesis will be tested at a one-sided 0.025 level of significance using a two-sample z-test of proportions.

- **CNS infarction** (NeuroARC defined) [evaluated at 30 days in the eITT analysis population]

The hypothesis is that the event rate for CNS infarction in the Intervention Group at 30 days will be lower than the Control Group at 30 days.

The formal null and alternative hypotheses to be tested are:

H_0: $\pi_{CNS-I} = \pi_{CNS-C}$

H_1: $\pi_{CNS-I} < \pi_{CNS-C}$

where π_{CNS-I} is the true rate of CNS infarction in the Intervention arm and π_{CNS-C} is the true rate of CNS infarction in the Control arm.

The null hypothesis will be tested at a one-sided 0.025 level of significance using a two-sample z-test of proportions.

- **Total volume of cerebral ischemic lesions** detected by DW-MRI, [evaluated 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

The hypothesis is that the total volume of cerebral ischemic lesions in the Intervention Group will be lower than the Control Group.

The formal null and alternative hypotheses to be tested are:

$$H_0: \pi_{TLV\text{-}I} = \pi_{TLV\text{-}C}$$

$$H_1: \pi_{TLV\text{-}I} < \pi_{TLV\text{-}C}$$

where $\pi_{TLV\text{-}I}$ is the true total volume of cerebral ischemic lesions in the Intervention arm and $\pi_{TLV\text{-}C}$ is the true total volume of cerebral ischemic lesions in the Control arm.

The null hypothesis will be tested at a one-sided 0.025 level of significance using the two-sample z-test.

12.2.2 **Expected Control Primary Safety Endpoint Event Rate**

An expected event rate for the control group was determined based on published data from subjects undergoing unprotected TAVI.

A search of bibliographic scientific databases (PubMed and EMBASE) was undertaken to identify studies reporting VARC combined safety outcomes using the following search parameters:

- Language = English, species = humans
- Publication date January 2011 (publication of original VARC definitions) to present
- Keywords included: Valve Academic Research Consortium or VARC; aortic valve; and percutaneous, transcatheter, transluminal, transarterial, transfemoral, or transapical

Results were evaluated according to the following selection criteria:

- Peer-reviewed publications only. Abstracts, case reports, conference presentations, editorials, and expert opinions were excluded.
- Reported using VARC or VARC-2 definitions (explicitly mentioned in text), and reported VARC combined safety endpoint or the VARC-2 early safety endpoint at 30 days
- N≥20 (studies reporting outcomes in fewer than 20 TAVI subjects were excluded)
- Patients with severe AS undergoing TAVI with Medtronic or Edwards valves. Studies reporting outcomes exclusively in valve-in valve or subjects undergoing TAVI via any approach other than transfemoral or transapical (e.g., transaxillary, transsubclavian, direct aortic) were excluded. When larger cohorts included these subjects, the results in these subjects were excluded when data allowed; otherwise they were included.
- Publications with overlapping data were identified where possible, and the most recent procedural timeframe (or largest N) was used and the other(s) discarded.

Additional relevant studies were identified through a manual search of secondary sources, including the bibliographies of initially identified articles and review articles and commentaries.

Although the primary safety endpoint is the VARC-2[1] early safety endpoint, which differs from the original VARC definition[78], studies reporting either composite endpoint were collected and

evaluated to inform determination of the PG. Based on differences between the definitions (see Table 9 below), we would expect the VARC-2 event rate to be slightly higher based on the addition of all stroke and Stage 2 acute kidney injury; however, more published data according to the earlier VARC definitions is likely available.

Table 9. Comparison of VARC and VARC-2 Early Safety Endpoint Components

VARC[78] **Combined Safety Endpoint (at 30 days)**	**VARC-2[1]** **Early Safety (at 30 days)**
• All-cause mortality • **Major stroke** • Life-threatening (or disabling) bleeding • **Acute kidney injury – Stage 3 (including renal replacement therapy)** • Coronary artery obstruction requiring intervention • Major vascular complication • Repeat procedure for valve-related dysfunction (surgical or interventional therapy) • **Peri-procedural MI**	• All-cause mortality • **All stroke (disabling and non-disabling)** • Life-threatening bleeding • **Acute kidney injury – Stage 2 or 3 (including renal replacement therapy)** • Coronary artery obstruction requiring intervention • Major vascular complication • Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
Note: Bold text indicates differences between the two definitions. This table represents an overall comparison; details of individual component definitions have also changed between consensus documents.	

The literature search and sift identified a total of 19 studies reporting the original VARC combined safety endpoint and 6 studies reporting the VARC-2 early safety endpoint (Table 10 below).

Table 10. Published Combined Safety Event Rates at 30 days after Unprotected TAVI

Study	**N**	**Event Rate (%)**
VARC 1 Combined Safety		
Abdel-Wahab 2012[79]	70	13.0
Buchanan 2011[80]	305	38.2
D'Ascenzo 2013[81]	377	28.9
Dubois 2013[82]	73	29.0
van der Boon 2014[83]	882	26.6
Eltchaninoff 2012[84]	190	16.3
Gurvitch 2011[85]	310	18.4
Hammerer 2012[86]	50	18.0
Hayashida 2012[87]	260	17.3
van der Boon 2013[88]	298	23.5
Scherner 2012[89]	150	28.0
Seiffert 2013[90]	326	21.2
Stahli 2011[91]	130	20.8
Ussia 2012[92]	181	25.8

Wenaweser 2011[93]	256	29.3
Yamamoto 2013[94]	415	16.4
Abramowitz 2014[95]	249	6.8
Greif 2014[96]	461	12.6
Sabate 2013[97]	1416	14.0
Simple mean	337	23.8
Weighted mean	--	20.4
VARC 2 Early Safety		
D'Onofrio 2013[98]	774	21.7
Tarantini 2013[99]	250	21.2
Chopard 2014[100]	3928	40.4
Conradi 2013[101]	100	19.0
Magri 2013[102]	330	30.9
Seco 2014[103]	32	21.9
Simple mean	902	25.9
Weighted mean	--	35.8

The above studies represent the best estimation of the expected event rate in the population of subjects with severe AS undergoing TAVI via the transfemoral or transapical route with Edwards or Medtronic valve systems. The average event rate in studies reporting outcomes according to the VARC-2 definition (the primary safety endpoint for the REFLECT Trial) was 25.9%; among studies reporting the slightly more circumscribed VARC 1 definition, the average event rate was 23.8%. Therefore, the expected event rate of the primary safety endpoint in the Control group was estimated at 25%.

12.2.3 **Expected Primary Efficacy Endpoint Event Rate**

Occurrence of the components of the primary hierarchical composite efficacy endpoint was estimated based on published literature and special consideration of data from the DEFLECT III randomized controlled trial of the TriGuard device:

For Tier 1 of the hierarchy, an expected event rate of all-cause mortality or stroke (disabling and non-disabling) at 30 days was estimated based on published data from randomized controlled trials of subjects undergoing unprotected TAVI (Table 11).

Table 11. Composite of all-cause mortality and any stroke (30 days) in unprotected TAVI RCTs

Trial	N	Composite		Component					
		Death + All Stroke	Death + Disabling Stroke	Death	All Stroke	All stroke or TIA	Disabling / Major Stroke	Non-disabling / Minor Stroke	TIA
PARTNER 1A (High Risk)[4]*	348	*7.8% (27)*	6.9% (24)	3.4% (12)	4.6% (16)	5.5%(19)	3.8% (13)	0.9% (3)	0.9% (3)
PARTNER 1B (Inoperable)[5]	179	*10.1% (18)*	8.4% (15)	5.0% (9)	6.7% (12)	6.7% (12)	5.0% (9)	1.7% (3)	0% (0)

CoreValve High Risk[6]*	390	*6.9% (27)*	5.9% (23)	3.3% (13)	4.9% (19)	*5.9% (23)*	3.9% (15)	1.0% (4)	0.8% (3)
CoreValve Extreme Risk[7]*	489	*11.5% (56)*	9.8% (48)	8.4% (41)	4.0% (19)	*4.5% (22)*	2.3% (11)	1.9% (9)	0.6% (3)
Simple average	9.1%								
Weighted average	9.1%								
Meta-analytic average	8.8%								

NOTE: *Italics* indicates that the event rate is not directly reported, but the given percentage represents a best estimate based on component event rates; for the composite of death and all stroke, it is assumed that no subject with a non-disabling stroke also experienced a death or disabling stroke within the 30-day timeframe (with the exception of CoreValve Extreme, in which data indicates that 1 subject experienced both a major and a minor stroke).

*Percentages given are Kaplan Meier estimates, and therefore do not equal the number of subjects experiencing an event divided by the total number of subjects

In addition, we took into account randomized control trials of subjects randomized to TAVI with vs. without protection device (table 11a).

Table 11a. Rates of death and Stroke at 30 days in RCTs of protection devices.

Trial*	N	Death at 30 days		Stroke at 30 days	
		Device	Control	Device	Control
DEFLECT III[8] 2015	85	2.17%	5.13%	4.35%	5.13%
EMBOL-X[72] 2015	30	0%	0%	--	--
MISTRAL-C[73] 2016	65	3.12%	9.09%	0%	6.06%
CLEAN TAVI[74] 2016	100	0%	2%	8%	8%
SENTINEL[9] 2017	363	1.28%	1.8%	5.63%	9.09%
Simple mean		1.32%	3.6%	3.6%	5.66%
Weighted mean		1.33%	3.21%	5.09%	7.25%
Meta-analytic mean*		1.6%	3.83%	5.09%	7.26%

* Embol-X excluded

A recently published letter[104] presented a meta-analysis of the above trials for the primary end point of death and stroke at longest follow-up available, showed rates of 6% vs 10% for device vs. control respectively.

Based on the above, and considering SENTINEL being the most recent trial (with up to 9% stroke rate and 1.8% death rate in the controls), we conservatively estimate an ~11% rate of all-cause mortality or stroke at 30 days in subjects undergoing unprotected TAVI and a 50% reduction yielding a ~6% assumed event rate in the protected group.

The remaining component event rates (Tiers 2-4) are estimated based on data from the above mentioned trials, which employed identical NIHSS assessments and DW-MRI analysis methodology.

We conservatively expect 9% of controls and 6% of device group patients to have any NIHSS worsening (table 6b).

Among subjects who survived free of stroke to 30 days, and who did not experience NIHSS worsening at the post-procedure (2-5 days post-procedure) assessment (Tier 3 of the hierarchy), we expect 11% of controls and 27% of device group patients to be free of any lesions on MRI. These assumptions are based on the above trials and more specifically on the published results of DEFLECT III[8] (Per Treatment) which used a similar device with full cerebral protection (as opposed to SENTINEL) and the same MRI assessment modality as planned in this trial (see also table 6a).

Among patients surviving without stroke at 30 days, and who did not experience NIHSS worsening, and who had MRI lesions on DW-MRI (final 4th Tier) we expect the rates of lesion volumes categorized by size in pre-specified set ranges of >0-50 mm^3, >50-150 mm^3 and above 150 mm^3 to be 7%, 33%, and 48% in the controls, respectively, and 19%, 7.5% and 46% in the device arm, respectively. Expected rates were adapted from DEFLECT III (Per Treatment), the only published study thus far to incorporate such volume subdivisions.[8]

All tiers and their respective assumed rates are presented in table 11b.

Table 11b. Assumed event rates

	Assumed Control Rates	**Assumed TriGUARD *3* Rates**
Death or Stroke	11%	6%
Worsening NIHSS	9%	6%
Freedom from MRI Findings (Lesion Volume 0 mm^3)	11%	27%
Lesion Volume (mm^3)		
>0-50	7%	19%
>50-150	33%	7.5%
> 150	48%	46%

15% Missing in MRI Follow-up and 5% missing for all other parameters

Type I Error = 5%

The primary analysis population for the primary endpoint is the efficacy Intention to Treat (eITT) population (§12.3.1), which excludes subjects with conversion to surgery or prolonged cardiac arrest prior to the post-procedure DW-MRI. Selection of this population as the primary analysis population for the efficacy endpoint ensures that, should a small number of subjects experience an adverse endpoint event due to circumstances unrelated to procedural neuroprotection, the study will remain powered to detect a clinically-meaningful treatment effect, particularly regarding the volume of subclinical cerebral ischemic lesions on DW-MRI.

12.2.4 **Sample Size Estimation**

12.2.4.1.1 Primary Safety Endpoint

The primary safety endpoint is combined safety (VARC-2 defined as a composite of death, stroke, life-threatening or disabling bleeding, acute kidney injury [Stage 2 or 3], coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure), evaluated at 30 days.

Based on published literature of patients undergoing unprotected TAVI (§12.2.2), establishing the expected Control event rate of 25%, and a 37.5% relative margin (absolute delta 9.4%), a Performance Goal (PG) has been has been set at 34.4% (25% + 9.4%). The primary safety analysis will assess if the Intervention group's safety event rate is significantly less than the PG of 34.4%.

A sample size of 179 evaluable subjects in the intervention group will provide 85% power to determine whether the intervention group meets the PG at the one-sided alpha=0.05 level when using a one-sample z-test of proportions. After accounting for a potential 5% loss to clinical follow-up or dropout from the primary analysis population (As Treated) at 30 days, the total required sample size is 190 subjects in each intervention group. Therefore, the initial randomized sample size of 190 subjects in each intervention group in each phase will have sufficient power to determine whether the intervention meets the safety PG. For Phase II 150 subjects randomized to the TriGUARD *3* and 40- 50 roll-ins will constitute the primary safety population.

12.2.4.1.2 Primary Efficacy Endpoint

Sample size for assessing superiority of Intervention over Control with respect to the hierarchical composite primary efficacy endpoint was estimated using the following assumptions:

- All-cause mortality or any stroke at 30 days will occur in ~11% of Control subjects and ~6% of Intervention subjects (5% absolute reduction, ~45% relative reduction)
- Among subjects without all-cause mortality or any stroke to 30 days, NIHSS worsening 2-5 days post-procedure will occur in 9% of Control subjects and 6% of Intervention subjects (3% absolute reduction, 33.3% relative reduction)
- Among subjects without all-cause mortality or any stroke to 30 days and without NIHSS worsening 2-5 days post-procedure, MRI findings will occur in 89% of Control subjects and in 73% of intervention subjects (16% absolute reduction, 17.9% relative reduction).
- Among subjects without all-cause mortality or any stroke to 30 days, without NIHSS worsening 2-5 days post procedure, but with MRI findings, lesion volumes can be divided into 3 out of 4 subsets- 0 mm^3, >0-50 mm^3, >50-150 mm^3 and >150 mm^3 . For these volume subsets, we expect rates of 11%, 7%, 33% and 48%, respectively, in the control group and 27%, 19%, 7.5%, and 46%, respectively, in the intervention group.
- For sample size calculations a relative reduction of 30% is expected in each lesion volume subset, based on the comparison of total lesion volumes between device and control groups in DEFLECT I, MISTRAL C[73] SENTINEL[9] and CLEAN-TAVI[74].
- The smallest detectable difference in MRI is a single voxel. In addition, inter-rater mean differences between two independent observers was 15% or ~5 voxels (40.5 mm^3) in the KSH Methodology/Reproducibility Study (data on file). Accordingly, a meaningful difference to declare a win/lose between MRI lesion volumes was set at a 15% relative difference or a 50 mm^3 absolute difference.

- Loss to post-procedure DW-MRI follow-up is expected to occur in 15% of all subjects (due to contraindications to post-procedure DW-MRI [e.g., pacemaker implantation] or subject non-compliance)
- Loss to follow-up for all other reasons is expected to be 5%.
- Overall α (one-sided)=0.025; (see §12.4.2)

To determine the required sample size, calculations were performed by simulating 5000 samples on SAS software postulating the above parameters; mortality and stroke rates and proportions of patients with NIHSS worsening, any MRI lesions and volumes divided to subsets were simulated by a random binary function.

An evaluable sample size of 225 subjects (2:1 randomization with 150 in the Intervention group and 75 new Control subjects) is sufficient to demonstrate superiority of the Intervention group to the Control group for the primary efficacy endpoint when pair-wise comparisons are made between subjects using the Finkelstein-Schoenfeld method,[2] and outcomes between treatment groups are compared by the chi-square test.

Therefore, the initial randomized cohort sample size of 225 subjects (150 in the Intervention group and 75 new control subjects) will have >80% power to demonstrate superiority of the Intervention group for the primary efficacy endpoint (one sided α=0.025). Notably, in several simulations, considering different distributions for lesion volume and different distributions for death/ stroke, the study power remained greater than 80%.

Adding the 63 control subjects already enrolled in REFLECT Phase I for a total of 138 control subjects would increase the power to at least 92% to demonstrate superiority of the primary efficacy endpoint. 5% loss to follow up is included.

12.3 Analysis Populations

12.3.1 **Efficacy Intention to Treat (eITT) Analysis Population**

The efficacy Intention to Treat (eITT) analysis population is defined as:

- Subjects who are enrolled in the trial and randomized to a treatment group, regardless of treatment actually received AND
- Who do not have conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI

The eITT population of evaluable (i.e., not Roll-In) subjects will be used for the primary analysis of the primary efficacy endpoint, the primary analysis of the secondary hypothesis-driven endpoints, and the primary analysis of all secondary neurologic efficacy endpoints.

12.3.2 **Intention to Treat Analysis Population**

The Intention To Treat (ITT) analysis population is defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received.

The ITT population of evaluable (i.e., not Roll-In) subjects will be used for the primary analysis of secondary performance endpoints and Other Measures. The ITT population will also be used for a secondary analysis of the primary and secondary efficacy endpoints and the primary and secondary safety endpoints.

12.3.3 **As Treated Analysis Population**

The As Treated (AT) analysis population is defined by the treatment actually received, rather than the treatment assigned. In the AT population, subjects in whom vascular access in the

contralateral femoral artery has been established for the intended deployment of the TriGuard HDH or TriGUARD *3* device will be analyzed as part of the Intervention group, and subjects in whom the TAVI procedure is initiated (but no vascular access for intended deployment of the TriGuard HDH or TriGUARD *3* is established) will be analyzed as part of the Control group.

The AT population will be used for the primary analysis of all primary and secondary safety endpoints. The AT population will also be used as the secondary analysis population for the secondary performance endpoints and Other Measures.

12.3.4 **Per Treatment Population**

The Per Treatment (PT) analysis population is defined as subjects in the Intervention group in whom device positioning is maintained until final procedure with complete cerebral coverage, and all Control group subjects.

The PT population will be used for an additional analysis of the primary and secondary efficacy endpoints and other measures.

12.3.5 **Roll-In Patient Population**

The Roll-In (RI) patient population is defined as all subjects who undergo TAVI with the TriGuard HDH or TriGUARD *3* prior to enrollment of the first evaluable subject at each investigational site. Each investigational site without prior experience with the TriGuard device (minimum of 2 prior cases) will enroll a minimum of 2 RI subjects. RI subjects will not be randomized to a treatment arm, but will undergo TAVI with the embolic protection device and will undergo all protocol-specified follow-ups.

For the purposes of analysis, a subject is considered enrolled in the Roll-In phase of the study when:

- The patient has been judged to meet all inclusion and no exclusion criteria, and has signed a Patient Informed Consent form
- The TriGuard HDH of TriGUARD *3* device has been introduced into the patient's bloodstream

The RI patient population will be used for a separate analysis of all primary and secondary endpoints and Other Measures. Additional analyses will evaluate primary and secondary endpoints in the pooled population of RI Subjects plus Evaluable Subjects.

12.4 Method of Analysis and Reporting

12.4.1 **Baseline Characteristics**

The following data will be summarized using descriptive statistics and presented by treatment group for eITT (Roll-In subjects are excluded), ITT (Roll-In subjects are excluded), AT (Roll-In subjects are excluded), PT (Roll-In subjects are excluded), and Roll-In analysis sets. Descriptive statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group.

- Baseline demographics
- Baseline comorbidities, risk factors and medical history
- Cardiac risk factors, angina status and cardiac history
- Procedural characteristics

- Device details

12.4.2 **Primary Safety Endpoint**

The primary safety hypothesis is that the rate of the Combined Safety Endpoint (defined according to VARC 2 as the composite of death, stroke, life-threatening or disabling bleeding, AKI [Stage 2/3], coronary artery obstruction requiring intervention, major vascular complication, and valve-related dysfunction requiring repeat procedure) at 30 days in the group undergoing TAVI with the TriGuard HDH or TriGUARD *3* system (Intervention group) is significantly less than the Performance Goal (PG). The following analysis will be carried out in the AT (primary analysis population) and ITT populations including Roll-ins.

The primary safety analysis will assess if the Intervention group's safety endpoint rate is significantly less than 34.4% using a one-sample z-test of proportions. Specifically, the null and alternative hypotheses to be tested are:

$$H_0: \pi \geq 0.344$$

$$H_1: \pi < 0.344$$

where π is the true, unknown, safety event rate for the Intervention arm.

The number and percentage of patients in each group experiencing the safety endpoint rate will be presented for each treatment; in addition, one-sided 95% confidence intervals of the percentage will be presented, based on the normal approximation to the binomial distribution. For the intervention group, the above null hypothesis will be carried out at a one-sided 0.05 level of significance using the one-sample z-test of proportions. Only AT and ITT patients who experienced a safety endpoint or had at least 23 days (30 days minus the allowable 7 day visit window) of follow-up will be included in the analyses.

As a secondary analysis, to account for any missing data in the primary endpoint (caused by not experiencing the safety endpoint AND prematurely withdrawing from the study before 23 days of follow-up), a tipping point analysis will be conducted. Here the above safety null hypothesis will be repeatedly tested, first assuming 0 patients with missing data failed (i.e., experienced the safety event), then assuming 1 patient with missing data experienced the safety event, then assuming 2 patients with missing data experienced the safety event, etc. Of interest is the "tipping" point, i.e., the number of Intervention missing data subjects who must be imputed as failures in order for the safety null hypothesis to no longer be rejected.

In addition, in the final analysis, assessments of study-center and of region effect on the primary safety endpoint will be carried out on the interventional group within the AT population using logistic regressions. A 0.15 level of significance will be used to assess the significance of each of the study center and region effects on the safety endpoint. A non-significant result for each of study centers and regions will support the pooling of patients across study centers and across regions for the primary safety analysis. A significant result will require further inspection of the by-center and by-region results to assess if poolability is appropriate. Note that centers with less than 5 subjects will be pooled with other centers by closest geographic region; this pooling will be carried out prior to the unblinding.

In addition, a logistic regression to assess the consistency of the primary safety endpoint rate across the following categories will also be performed on the interventional arm (separately for Phase I and Phase II) within the AT population:

- Subject gender (male versus female)
- Valve prosthesis type (Edwards vs. Medtronic)

- Operative risk (by Society of Thoracic Surgeons [STS] Risk Score)
- Type and duration of antiplatelet therapy:
    - Pre- and peri-procedural therapy:
        - Protocol-recommended antiplatelet therapy vs. other
    - Maintenance therapy:
        - Dual antiplatelet therapy (DAPT) to 90 days vs.
        - Monotherapy (aspirin or clopidogrel) to 90 days vs.
        - Warfarin with antiplatelet therapy to 90 days vs.
        - Other

As above, a 0.15 level of significance will be used to assess the significance of the difference of the primary safety endpoint rate across the subgroups of each factor.

12.4.3 **Primary Efficacy Endpoint**

The primary hypothesis is that TAVI with the TriGuard HDH or TriGUARD *3* system is superior to standard (unprotected) TAVI for the primary hierarchical composite efficacy endpoint of all-cause mortality or any stroke at 30 days (Tier 1), followed by NIHSS worsening (increase from baseline) 2-5 days post-procedure (Tier 2), followed by any ischemic cerebral findings on DW-MRI (Tier 3), followed by total volume of post-procedure cerebral ischemic lesions detected by DW-MRI divided into preset subdivisions (Tier 4). Poolability of the Phase I and Phase II control subjects will be assessed at the time of the primary analysis and the results will determine the control population used for the primary analysis of the primary efficacy endpoint as detailed in the SAP.

The analytic approach is based on the statistical method described by Finkelstein and Schoenfeld.[2] A similar approach was used in PARTNER Trial (Cohort B) where the co-primary end point was hierarchical composite of the time to death from any cause or the time to the first occurrence of repeat hospitalization (after the index procedure) due to valve-related or procedure related clinical deterioration.[105] In addition, this approach was further explored and recommended for cardiovascular trials by Pocock et al.[77]

In brief, we propose the following analysis methodology:

Each subject in the intervention group is compared with each and every subject from the control group based on the following prespecified hierarchy:

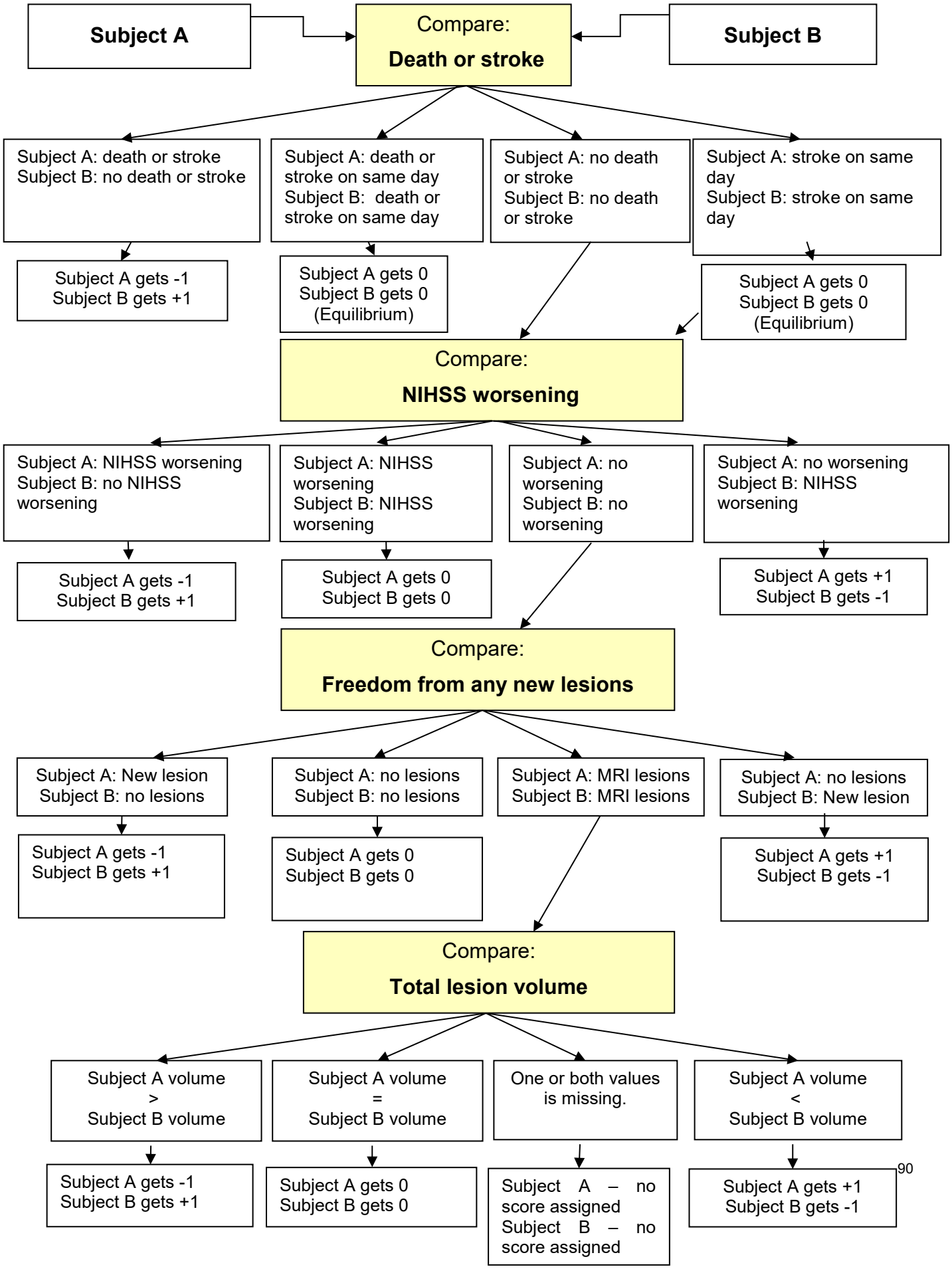
- All-cause mortality or any stroke (disabling or non-disabling) [evaluated at 30 days]
    - If both had a death/stroke a time to event analysis by days will determine a win
    - If both patients had a stroke at the same day the comparison moves to the next tier
- NIHSS worsening (increase from baseline) [evaluated at post-procedure (2 to 5 days post-procedure)]
- Freedom from any cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure
- Total volume of cerebral ischemic lesions detected by diffusion-weighted magnetic resonance imaging (DW-MRI) 2 to 5 days post-procedure

For example:

- If Subject A has stroke and Subject B survives free of stroke or death to 30 days, Subject B wins (score +1) and Subject A loses (score -1).
- If Subject A and Subject B both have death/stroke, time to event by day will determine a win.
- If both had a stroke on same day, the comparison moves on to the next tier.
- Assuming neither experiences a stroke or death before 30 days, if Subject A experiences NIHSS worsening, and Subject B does not experience NIHSS worsening, Subject A loses (score -1) and Subject B wins (score +1). In case both have NIHSS worsening the patient with the lesser worsening wins.
- Assuming neither subject experiences a stroke or death before 30 days or NIHSS worsening from baseline, if Subject A has no cerebral ischemic lesions on DW-MRI and Subject B has a cerebral ischemic lesion on DW-MRI, Subject A wins (score +1) and Subject B loses (Score -1).
- Assuming neither subject experiences a stroke or death before 30 days, NIHSS worsening from baseline or freedom from DW-MRI cerebral ischemic lesions, if Subject A has a total cerebral ischemic lesion volume of 50 mm^3 and Subject B has a total cerebral ischemic lesion volume of 100 mm^3, Subject A wins (score +1) and Subject B loses (Score -1).

An illustration of this algorithm is provided in Figure 4 below.

Figure 4. Algorithm of assigning scores by the Finkelstein and Schoenfeld method (*Note: each patient from the intervention group is compared with each and every patient from the control group*)



After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared by chi-square test.

This analytic approach does not result in a natural point-estimate (e.g., proportion, mean, median, time-to-event); however, Pocock et al. provided a computational framework for the test statistic called “win ratio". In brief, it is calculated as a proportion of "wins" for each group out of the total number of the pairwise comparisons.

No imputation of missing DW-MRI data will be performed for the primary analysis. However, in order to assess the sensitivity of results to missing DW-MRI data, multiple imputations with the linear regression approach will be used as the secondary sensitivity analysis. This assessment is necessary because the rate of permanent pacemaker implantation (causing loss to DW-MRI follow-up) may vary according to patient clinical characteristics and prosthesis type.[106] Specifically, missing total volume of cerebral ischemic lesions on post-procedure diffusion-weighted MRI will be imputed via multiple imputation linear regression (10 imputed data sets will be created). The covariates used for the imputation model will be treatment group, age at time of enrollment, body mass index, race, smoking status, creatinine level, hyperlipidemia, hypertension, aortic arch disease burden, porcelain aorta, aortic valve area at baseline, procedure time, country, valve type, balloon post dilatation, arch type, and level of calcification. This creation of the 10 datasets will be carried out using PROC MI in SAS. For each data set, the above-mentioned chi-square test will be carried out on the primary endpoint and one overall chi-square result will be generated from the 10 datasets. For each patient with missing TLV, the crux of multiple imputation is to estimate TLV from patients with non-missing TLV who have similar baseline characteristics as the patient with missing TLV. Thus, in essence, TLV for high risk patients with missing TLV due to pacemaker will theoretically be estimated from patients with similar high risk profiles who do not have pacemakers.

The assumptions for powering the primary efficacy endpoint are based on neurologic, and imaging data from a limited number of subjects in the above mentioned RCTs (§12.2.2). In Phase I due to uncertainty regarding the primary efficacy endpoint, an unblinded interim analysis was planned to be conducted to re-evaluate the sample size required to demonstrate superiority of the Intervention group to the Control group. The unblinded interim analysis was planned to be conducted when 90 subjects total who meet the eITT population definition have completed the 30-day follow-up visit. This interim analysis was to be inspected by an independent data safety and monitoring Board (DSMB) and the unblinded results will not be made privy to the sponsor, investigator, or any REFLECT team member, even in the event of a DSMB recommendation of an increase in sample size (i.e., the sponsor will not be made privy to the reason for any DSMB recommendation of an increase in sample size). If the interim analysis would have determined that more than 285 randomized subjects will be required to ensure adequate study power, enrollment would have continued (contingent on DSMB recommendation and prior FDA approval, and at the Sponsor’s discretion) until the required number of subjects would have been enrolled, or until the total subject limit for the study has been reached (whichever occurs first).

Specifically, at the interim analysis in Phase I, the trial sample size was to be re-calculated, if necessary, to ensure 80% conditional power to demonstrate superiority (overall 2-sided α=0.05) of the Intervention group to the control group for the primary efficacy endpoint, conditioned on the interim unblinded results and loss to DW-MRI follow-up, according to the eITT population definition (there will be no imputation of missing data in this interim analysis; i.e., missing data will be excluded; also, sample size can only be increased at this interim

stage; it will not be decreased beyond what is currently planned). The conditional power and sample size re-calculation for the final analysis were to be ascertained by computer simulations and by established methodology outlined in Chen, DeMets and Lan.[10] i.e., at the interim stage, we were to use Monte Carlo simulations to assess the conditional power of achieving a significant Mann-Whitney test by the end of the study, conditioned on the distribution of the observed interim data. If the conditional power is 50% - 80% (the "promising zone" according to Chen, DeMets and Lan), we were to use simulations to ascertain the increase in sample size required to yield 80% conditional power for the Mann-Whitney test. If the conditional power was determined to be <50% or >80%, the study was to proceed as is without a sample size adjustment (i.e., only the initial randomized cohort of 225 subjects were to be enrolled). The above-mentioned computer simulations were to be carried out assuming the distribution of TLV data follows a negative binomial distribution within each treatment group. The intent of this analysis was to ensure adequate power to detect a clinically meaningful treatment effect at the end of the study by providing the option to increase the sample size if necessary.

There was no intention to stop the study for overwhelming efficacy at the interim analysis. However, as a precautionary measure and to be conservative (due to the presence of an unblinded interim analysis), the O'Brien Fleming alpha spending method was to be used to calculate an alpha penalty for the final analysis regardless of whether a sample size increase is needed (final analysis two-sided alpha = 0.049).

NOTE: A revised adaptive design has been developed for Phase II of the study to inform a potential sample size increase based on interim conditional power; for details, please refer to §12.1.1.

In the final analysis, assessment of treatment-by-study-center and treatment-by-region on the primary efficacy endpoint will be carried out on the eITT population using quantile regression. Total score obtained for each subject using the proposed approach (Finkelstein and Schoenfeld) will be the model dependent variable. The following two models will be built: 1.) Model inclusive of treatment, study center, and treatment-by-study center interaction, and 2.) Treatment region (US versus OUS, Phase I only), and treatment-by-region interaction. A 0.15 level of significance will be used to assess the significance of each of the study center and region effects on the efficacy endpoint. A non-significant result for each of study center and region will support the pooling of patients across study centers and across regions for the primary efficacy analysis. A significant result will require further inspection of the by-center and by-region results to assess if poolability is appropriate. Note that centers with less than 5 subjects will be pooled with other centers by closest geographic region; this pooling will be carried out prior to the unblinding.

Additionally, an assessment of treatment-by-study-center and treatment-by-region on each component of the primary efficacy endpoint will be carried out on the eITT population using analysis of variance on the cube root transformation for total lesion volume data and logistic regression for death/stroke and NIHSS worsening, with effects for 1.) Treatment, study center, and treatment-by-study center interaction, and 2.) Treatment, region (US versus OUS, Phase I only), and treatment-by-region interaction. As above, a 0.15 level of significance will be used to assess the significance of the interaction; a non-significant interaction or an interaction that is significant but only quantitative (and not qualitative) in nature will support the pooling of patients across study centers and across regions for the primary analysis; and centers with less than 5 subjects will be pooled with other centers by closest geographic region, with pooling carried out prior to the unblinding.

In addition, the above analysis will be repeated in the eITT population (separately in Phase I and Phase II analysis sets) to assess the consistency of treatment effects on each component of the primary efficacy endpoint across the following variables:

- Subject gender (male versus female)
- Valve prosthesis type (Edwards vs. Medtronic)
- Operative risk (by Society of Thoracic Surgeons [STS] Risk Score)
- Type and duration of antiplatelet therapy:
    - Pre- and peri-procedural therapy:
        - Protocol-recommended antiplatelet therapy vs. other
    - Maintenance therapy:
        - Dual antiplatelet therapy (DAPT) to 90 days vs.
        - Monotherapy (aspirin or clopidogrel) to 90 days vs.
        - Warfarin with antiplatelet therapy to 90 days vs.
        - Other

As above, analysis of variance on the cube root transformation for total lesion volume data and logistic regression for death/stroke and NIHSS worsening will be used, and a 0.15 level of significance will be used to assess the significance of the interaction.

If the primary efficacy endpoint is met in the primary (eITT) analysis population, sequential testing of the primary efficacy hypothesis will be conducted in the ITT analysis population of evaluable subjects (Roll-In patients are excluded.) As a secondary analysis, the primary efficacy endpoint and its components will be evaluated in the ITT analysis population of evaluable subjects (Roll-In patients are excluded). As an additional analysis, the primary efficacy endpoint will be evaluated in the PT population of subjects with available data.

An additional analysis of the primary efficacy endpoint will also be performed in the primary eITT analysis population with adjustment for pre-existing cerebral lesion volumes. The adjustment will be performed using a quantile regression with the resultant score being the dependent variable and group and the pre-existing cerebral lesion volumes will be independent. Specifically, the PROC QUANTREG procedure will be used to model the median of the score with QUANTILE=0.5 option.

12.4.4 **Hypothesis-driven Secondary Endpoints**

For the following secondary endpoints, a test for superiority of each intervention group to the control group will be performed. To address the issue of multiple tests among these secondary endpoints, sequential testing is planned. Secondary endpoints will be formally tested if and only if the primary study hypotheses are confirmed. The secondary endpoints will be tested individually, in the order in which they are listed as follows:

- **All stroke** [evaluated at 7 days in the eITT population]
- **NIHSS worsening**, defined as any NIHSS score increase from baseline [evaluated at 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]. A sensitivity analysis will further compare $\geq$2 points NIHSS worsening [evaluated at 2-5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

- **Composite of all-cause mortality and all stroke** [evaluated at 7 days in the eITT population]
- **CNS Infarction** (NeuroARC defined) [evaluated at 30 days in the eITT analysis population]
- **Total volume of cerebral ischemic lesions** detected by DW-MRI, [evaluated 2 to 5 days post-procedure in the efficacy Intention to Treat (eITT) analysis population]

The above endpoints will be tested by this pre-specified sequence, until the first non-significant difference is found between the two treatment groups. After that, other treatment comparisons will be examined in an exploratory manner.

12.4.5 **Exploratory Secondary Endpoints**

12.4.5.1.1 Secondary Safety Endpoints

All secondary safety endpoints, including the components of the primary safety endpoint will be reported by treatment group in the AT population of evaluable subjects using appropriate descriptive statistics (sample size, mean, standard deviation, median, minimum, maximum for continuous characteristics; counts and percentages of patients for dichotomous characteristics). No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints.

The AT analysis will be considered primary. As a secondary analysis, all secondary safety and performance endpoints will be evaluated in the ITT population of evaluable subjects.

For safety endpoints occurring in the Intervention and Roll-In groups, relationship to the investigational device/investigational procedure (as determined by an independent Clinical Events Committee [§11.1]) will also be reported.

12.4.5.1.2 Secondary Efficacy Endpoints

- Imaging Efficacy Endpoints

All secondary imaging efficacy endpoints will be reported by treatment group in the eITT Population of subjects with available data using descriptive statistics. No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints. Statistics for continuous variables will include mean, median, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group.

The eITT analysis will be considered primary. As a secondary analysis, all secondary imaging efficacy endpoints will be evaluated in the ITT population of evaluable subjects. An additional analysis will also be performed in the PT population.

An additional analysis of secondary imaging efficacy endpoints with adjustment for pre-existing cerebral lesion volume will also be performed in the primary eITT analysis population. These endpoints include presence of cerebral ischemic lesions (§□), number of cerebral ischemic lesions (§□), per-patient average single cerebral ischemic lesion volume (§□), single cerebral ischemic lesion volume (§□), and total volume of cerebral ischemic lesions (§□), which vary by their distribution from binary (as in "presence of cerebral ischemic lesions") to Poisson, or possibly negative binomial in others. The choice of a specific model used for adjustment will therefore depend on the actual distribution of the dependent variable (logistic, log-linear, Poisson, negative binomial or quantile). The models will include the study group and pre-existing cerebral lesion volume as independent variables.

- Neurologic Efficacy Endpoints

All secondary neurologic efficacy endpoints will be reported by treatment group in the eITT Population of evaluable subjects (Roll-In subjects are excluded) using descriptive statistics. No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints. Statistics for continuous variables will include mean, median, quartiles, standard deviation, minimum, maximum, and sample size for each treatment group. Binary variables will be summarized using frequencies, percentages, and sample size for each treatment group.

The analysis of the eITT population will be considered primary. As a secondary analysis, all secondary neurologic and cognitive efficacy endpoints will be evaluated in the ITT population of evaluable subjects. An additional analysis will also be performed in the PT population.

An additional analysis of secondary neurologic and cognitive efficacy endpoints with adjustment for pre-existing cerebral lesion volume will also be performed in the primary eITT analysis population. As in secondary imaging efficacy endpoints, the distribution of the neurologic endpoints (including NIHSS worsening [§□], and new neurologic impairment [§□]) varies. The models, therefore, will be chosen based on the actual distribution of dependent variable (logistic, log-linear, poisson, negative binomial or quantile), with study group variable and cerebral lesion volume as independent variable.

12.4.5.1.3 Secondary Performance Endpoints

All secondary performance endpoints will be reported by treatment group in the ITT population of evaluable subjects (RI subjects are excluded) using appropriate descriptive statistics (sample size, mean, standard deviation, median, minimum, maximum for continuous characteristics; counts and percentages of patients for dichotomous characteristics). No formal hypothesis testing will be performed, and there is no plan to adjust alpha to account for multiple testing of exploratory secondary endpoints.

The ITT analysis will be considered primary. As a secondary analysis, all secondary safety and performance endpoints will be evaluated in the AT population of evaluable subjects.

12.4.6 **Other Measures**

Other Measures will be reported by treatment group in the ITT population of evaluable subjects (RI subjects are excluded) using descriptive statistics. No formal hypothesis testing will be performed.

The ITT analysis will be considered primary. As a secondary analysis, Other Measures will be evaluated in the AT population of evaluable subjects. An additional analysis will also be performed in the PT population.

12.4.7 **Subgroup Analyses**

Subgroup analyses will be performed for all primary and secondary endpoints in their respective primary analysis populations for the following subgroups, and results will be reported by treatment group using descriptive statistics:

- Subjects with paroxysmal or persistent atrial fibrillation (AF) at baseline
- Subjects by valve prosthesis type (Edwards vs. Medtronic)

12.4.8 **Roll-In Population Analysis**

The Phase II Roll-In population will be pooled with the Phase II intervention group for the primary analysis of the primary safety endpoint. The Roll-In patient population will also be

used for a separate analysis of all primary and secondary endpoints and other measures. Additional analyses will evaluate primary and secondary endpoints in the pooled population of Roll-In Subjects plus Evaluable Subjects. The results of all analyses will be reported using descriptive statistics.

12.4.9 **Additional Analyses**

The following data will be summarized using descriptive statistics presented by treatment group:

- Subject enrollment and data compliance by site and visit (data compliance at each visit is percent of patients whose data forms have been collected and entered divided by the percent of patients whose forms should have been collected and entered) (ITT, eITT, PT, and AT populations)
- Frequency (number and percent of patients) with each type of concomitant medication (AT population)
- Frequency (number and percent of patients) with each site-reported Treatment Emergent AE overall and by MedDRA system organ class and preferred term (a treatment emergent AE is an AE that started or worsened during or after the index procedure) (AT population)
- Frequency (number and percent of patients) with each site-reported Treatment Emergent Serious AE overall and by MedDRA system organ class and preferred term (AT population)
- Frequency (number and percent of patients) with each site-reported Treatment Emergent AE or SAE, by CEC-adjudicated relationship to the investigational device or procedure (AT population)
- Protocol deviations (number and percentage of patients with each deviation type) (ITT population)
- Kaplan-Meier plots for MACCE and TAVI early safety through 30 days (AT Population; patients without an event will be censored at 30 days or day of withdrawal, whichever is earlier)
- Detailed listings on primary and secondary endpoints, site-reported AE as well as protocol deviations

13.0 Publication Policy

The Sponsor and the Principal Investigators are committed to the publication and widespread dissemination of the results of the study in the scientific community. This study represents a joint effort between the Sponsor and the Principal Investigators; as such, the parties agree that the recommendation of any party concerning manuscript or text shall be taken into consideration in the preparation of final scientific documents for publication or presentation.

All parties agree that the Investigators will prepare publications and/or presentations. The number of authors will be determined according to the rules of the addressed scientific journal and by decision of the investigators. Abstracts and articles shall be submitted to the Sponsor in advance of their publication. An agreement on the final form of abstracts and articles shall be obtained within an appropriate time frame of 60 days. In the event that diverging opinions on presentation of the data cannot be reconciled, the executive operation committee

consisting of one representative of the trial management team, the Sponsor and the Principal Investigators (or designated substitutes) will make a final decision.

Any and all information supplied or obtained during this study by or on behalf of any party involved in the study (in whatever form) shall be treated as confidential, shall not be disclosed to any third party unless with the prior written consent of the Sponsor in each case. Any documents, papers, drawings or other materials which are released or created by any party involved in this study are and shall remain at all times the property of the Sponsor excluding publications which are approved in writing by the Sponsor. Such materials shall not be reproduced in any form without the prior written consent of the Sponsor and must be returned to the Sponsor immediately upon request, or upon completion of the evaluation of such materials, whichever is the earlier.

All clinical data or any other information gathered during or after this Study related to the Study, people involved, or materials involved will be considered confidential. Confidential information will remain confidential for a period of 36 months following the study completion.

14.0 Data Collection and Monitoring

14.1 Data Collection and Monitoring

All required data for this study will be collected on standardized Case Report Forms (CRFs) using an electronic data capture system (EDC). The investigator (or designated hospital staff) will assure primary data collection based on source-documented hospital chart reviews.

Independent monitoring will be performed to ensure that the investigator and his/her study team conduct the clinical investigation in accordance with contract specifications, this protocol, the Declaration of Helsinki, ICH-GCP, ISO 14155, 21 CFR Part 812, and other applicable FDA and local regulations, and to ensure adequate protection of the rights and safety of subjects and the quality and integrity of the resulting data. Submitted trial data will be verified against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance with the pre-specified Monitoring Plan.

Progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the sponsor
- Telephone communications between site personnel (e.g., Site Investigator, Trial Coordinator) and trial monitors
- Review of CRFs and associated clinical records
- Review of regulatory documents

Responsible entities for monitoring in the US and EU respectively are listed in §3.0.

If a monitor becomes aware that an Investigator is not complying with the requirements mentioned above, the sponsor will be notified by the monitor. The sponsor will evaluate the non-compliance and if necessary, immediately either secure compliance or discontinue shipments of the investigational device to the Investigator and terminate the Investigator’s participation in continued enrolment in the investigation. The Investigator will be required to return all unused devices to the sponsor.

14.2 Source Documentation and Verification

Auditors, monitors, IRBs/ECs, the study sponsor, and the FDA and other regulatory authorities will have access to the medical records related to this study. Original or certified copies of all relevant clinical findings, observations, and other activities throughout the clinical investigation must be recorded and maintained in the medical file of each enrolled patient (no source documentation will be recorded directly on the CRF). At a minimum, the following must be included in each patient's file:

- Sufficient medical history and current physical condition, including any medication(s) the patient is taking at the time of the procedure to assess the patient's eligibility;
- The medical file should reveal the patient's participation in this study, including documentation of written informed consent;
- Dated report of the investigational procedure including medication, material usage, and complications, if applicable;
- Dated reports of the discharge and follow-up assessments;
- Dated results of required laboratory tests;
- Any adverse event(s), the resultant action or treatment, and outcome, if applicable; and
- In the case of withdrawal of patient consent, the reason and patient status at time of withdrawal.

The investigator will permit study-related monitoring, audits, IRB/EC review, and FDA and other applicable regulatory authority inspections by allowing direct access to the source data.

In case of electronic source data, periodic access will be allowed for full safety review. The review will be specific to study subjects and the records that would contain potential safety data. Dated print-outs are acceptable for preliminary review of safety information. Print-outs will not be limited to cardiac data only, but should include all available data related to the identified patient(s).

14.3 Record Retention

Sponsor and investigator will maintain records related to this study for 7 years (or longer according to local requirements) after the end of this study.

15.0 Ethical and Regulatory Considerations

15.1 Applicable Regulations

This trial will be conducted in compliance with the protocol, the sponsor's standard operating procedures and/or guidelines, FDA regulations, local regulations where applicable, ICH GCP guidelines, the Declaration of Helsinki, Annex X of the European Medical Devices Directive, and EN/ISO 14155:2011.

15.2 Institutional Review Board / Medical Ethics Committee

This trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The investigator will assure that an appropriately constituted Institutional Review Board (IRB) or Ethics Committee (EC) complies with the requirements of the International Conference on Harmonization Guideline. Prior to initiation of the study, the investigator will forward copies

of the protocol, Investigators Brochure, informed consent form and all other appendices to be used for the study to the IRB/EC for its review and approval. A copy of the written IRB/EC approval must be provided to the Sponsor (or designee) and should include the following:

- A statement of IRB/EC approval for the proposed study at the institution;
- The date the study was approved and the duration of approval (if applicable);
- Identification of the approved documents including version dates and/or other references. At a minimum, the following documents should be listed:
    - Study protocol
    - Patient information and consent form
    - Any additional written information to be provided to the patient
- A listing of any conditions attached to the approval (if applicable);
- Identification of the approved primary investigator;
- The signature of the IRB/EC chairperson;
- Acknowledgement of the sub-Investigators.

Any amendments to the protocol, as well as possible associated information and consent form changes, will be submitted to the IRB/EC and written approval obtained prior to implementation. Substantive changes will be submitted to the FDA for approval prior to implementation, and the FDA will be notified of any changes not requiring approval according to applicable guidelines.

15.3 Regulatory Approval

The Sponsor is responsible for notifying the study to the FDA and any other relevant authorities (as applicable) according to regulatory requirements. Investigators may not commence enrollment of subjects until they have met any local IRB/EC and hospital management requirements and have received confirmation from the Sponsor that the appropriate regulatory approvals have been obtained.

15.4 Trial Registration

This trial meets the definition of an “applicable clinical trial” according to Section 801 of the Food and Drug Administration Amendments Act. The Sponsor affirms that it will serve as the Responsible Party and fulfill all requirements regarding trial registration, the provision of clinical trial information, and results reporting through the ClinicalTrials.gov registry data bank.

Clinical trial information will be submitted no more than 21 days after the first subject is enrolled in the trial, and results information will be submitted no later than 1 year after completion of the trial or no later than 30 days after the device is approved, licensed, or cleared by the FDA.

15.5 Records and Reports

15.5.1 **Responsibilities of the Sponsor**

The Sponsor must maintain the following records:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement

- *Curriculum vitae* for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms prepared and signed by the Investigators and received source documentation and core lab reports
- Clinical Investigation Plan (CIP) and any amendments
- Investigators Brochure / Report of Prior Investigations
- Site monitoring reports
- Financial disclosure information

The Sponsor is responsible for the preparation of, the accuracy of the data contained in, and the review and submission of the reports listed in Table 12.

Table 12. Sponsor Reporting Responsibilities

Report	Submit To	Description
(confirmed) UADE	IRB/EC, Investigators, FDA, Other Regulatory (as applicable)	Sponsor will report on any confirmed UADE within 10 working days of notice receipt [21 CFR 812.150]
Withdrawal of IRB/EC approval	IRB/EC, Investigators, FDA, Other Regulatory (as applicable)	Notification, when appropriate, will be made with 5 working days of notice receipt.
Withdrawal of FDA/other regulatory approval	IRB/EC, Investigators	Notification, when appropriate, will be made with 5 working days of notice receipt.
Current investigator list	FDA	Sponsor will submit a list of the names and addresses of all investigators at 6 month intervals, beginning 6 months after FDA IDE approval.
Progress report	IRB/EC, Investigators, FDA	Annual
Recall and device disposition	IRB/EC, Investigators, FDA	Notification and explanation will be made within 30 days of the Sponsor's request that an Investigator return, repair, or otherwise dispose of any devices.
Final Report	IRB/EC, Investigators, FDA, Notified Bodies and Other Regulatory (as applicable)	Notification will be made within 30 working days of trial completion or termination. A final report will be submitted within 6 months of trial completion or termination.
Failure to obtain Informed Consent	FDA	Notification will be made within 5 working days after Sponsor's receipt of notification that Informed Consent was not obtained.
Emergency deviation from Clinical Investigation Plan (CIP)	FDA	Notification will be made within 5 working days after Sponsor's receipt of notification that an emergency deviation from the CIP was made to protect the life or physical well-being of a subject.

15.5.2 **Responsibilities of the Investigator**

Each Site Investigator is responsible for the preparation, review, signature, and retention of the records below:

- All essential correspondence related to the clinical trial
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation).
- Signed Investigator Agreement
- *Curriculum vitae*
- Clinical Investigation Plan (CIP) and any amendments

The investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 13. These are also subject to inspection by regulatory authorities and must be retained as specified in the CIP. The investigator may delegate responsibility for record maintenance to a member of his/her study team, but remains the ultimate responsible person.

Table 13. Investigator Reporting Responsibilities

Report	Submit To	Description
(potential) UADE	Sponsor, IRB/EC	Submit immediately via EDC CRF and via telephone. UADE must be submitted as soon as possible, but no later than 5 working days after first learning of the event.
SAE	Sponsor	Submit within 3 working days of first learning of the event (via EDC CRF).
SADE	Sponsor	Within 48 hours (if required by local or national regulations; otherwise, report as SAE)
Withdrawal of IRB/EC approval	Sponsor	Submit within 5 working days.
Failure to obtain Informed Consent	Sponsor, IRB/EC	Submit within 5 working days of subject exposure to device.
Emergency deviation from CIP	Sponsor, IRB/EC	Submit within 5 working days.
Planned deviation from CIP	Sponsor, IRB/EC, FDA	If the deviation affects the scientific soundness of the trial or the rights, safety, or welfare or the subject, and is not an emergency, prior approval must be obtained from the Sponsor, the IRB/EC, and the FDA.
Other deviation from CIP	Sponsor	Uncontrollable deviations (e.g., loss to follow-up) or deviations that do not affect the scientific soundness of the trial or the rights, safety, or welfare of the subject, and that are not an emergency, should be submitted as identified by the site or the Sponsor (or designee).

15.6 Protocol Amendments

Any protocol amendments will be approved by the Sponsor, the Principal Investigator, the IRB/EC and any necessary regulatory body before it can be implemented. Substantive changes will be submitted to the FDA for approval prior to implementation, and the FDA will be notified of any changes not requiring approval according to applicable guidelines.

15.7 Informed Consent

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patient in accordance with 21 CFR Part 50. The patient must sign the consent form prior to enrollment. This form or a modification based on local IRB/EC recommendations must be presented to and signed by all enrolled patients and signed by the principal investigator, sub-investigator or designated research staff in accordance with approving IRB/EC guidelines.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the investigator or assigned designee. Patients should not be coerced, persuaded, or unduly influenced to participate or remain in the trial. A subject or his/her legal representative must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the satisfaction of the subject or the representative.

Prior to participation in the trial, the written informed consent form should be signed and personally dated by the subject or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). If the subject or his/her legal representative is unable to read the consent form, a witness should be present during the entire informed consent discussion. After the informed consent form is read to the subject and signed by the subject or his/her legal representative, the witness should also sign the consent form, attesting that informed consent was freely given by the subject or his/her legal representative. For non-English speaking subjects, the written informed consent should be translated into the subject's native language, or a short form (including the elements of informed consent translated into the subject's native language) should be used. The informed consent process should be documented in each subject's medical record.

The subject or his/her legal representative must receive a copy of the signed and dated informed consent form.

The Investigator shall inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required, that may be relevant to the subject and his/her willingness to continue participation in the study. The consent form should be updated or amended whenever such new information becomes available and updated consent shall be recorded.

15.8 Termination of the Study

Keystone Heart Ltd. reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Possible reasons for early trial termination include:

- Unanticipated Adverse Device Effects (UADEs) present an unreasonable risk to patients
- Recommendation from the DSMB

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the IRBs/ECs. The Sponsor will also inform the FDA and the relevant Competent Authority (where required). In the case of early termination of trial enrollment, follow-up visits will continue for all enrolled subjects.

The Sponsor may terminate an investigator's or site's participation in the study if there is evidence of an investigator's failure to maintain adequate clinical standards or evidence of an investigator or staff's failure to comply with the protocol. Should investigator or site

participation be considered for termination, the Sponsor (or designee) will ensure appropriate follow-up for any subjects enrolled, including transferal to the supervision of an approved investigator and approval of transfer of subject oversight and follow-up by the appropriate IRB/EC. Notification of study site suspension or termination will occur no later than five (5) working days after the Sponsor makes the determination. A suspended or terminated study site may not be reinitiated without approval of the reviewing IRB/EC. The investigator should notify the IRB/EC in writing as soon as possible but no later than within 10 days if the premature termination is related to safety or compliance issues. The same procedure will be applied to the Competent Authority where required.

15.9 Auditing

As a quality assurance measure, the site may be audited during the course of the ongoing clinical trial as well as following completion of the trial. The purpose of an audit is to provide an independent evaluation separate from routine monitoring or quality control functions of trial conduct and protocol and GCP compliance. The audit may be conducted by Keystone Heart Ltd personnel (or designee), the FDA, or another regulatory body. Please notify the Sponsor if the FDA or another regulatory body requests an audit. The site investigator and/or institution shall permit Keystone Heart Ltd. and regulatory bodies direct access to source data and documents.

15.10 Patient Privacy

Keystone Heart Ltd affirms and upholds the principle of patient confidentiality. Throughout this study, all data forwarded to Keystone Heart Ltd. or its designee will only be identified by a study-specific subject identification number. “Protected Health Information” will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), and all personal data of EU individuals will be protected in compliance with the EU-US Privacy Shield Principles (12.7.2016).

The investigator agrees that representatives of Keystone Heart Ltd., the contract research organizations and regulatory authorities may inspect included patients’ records to verify trial data, provide the data are treated as confidential and that the subject’s privacy is guaranteed.

16.0 Appendices

16.1 Appendix I: Definitions

Acute cardiovascular surgery

An immediate transfer from the catheterization lab to the operative room during the initial treatment phase due to the need for emergency coronary artery bypass graft surgery, cardiac valve surgery, or other vascular surgical intervention.

Access related

Any adverse clinical consequence possibly associated with any of the access sites used during the procedure.

Access site

Any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath, including the left ventricular (LV) apex and the aorta.

Acute Kidney Injury (AKI),

[AKIN classification]

Change in serum creatinine (up to 7 days) compared with baseline:[35]

- **Stage 1:**
  - Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR
  - Urine output <0.5 ml/kg per hour for >6 but <12 hours
- **Stage 2**:
  - Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) OR
  - Urine output <0.5 ml/kg per hour for >12 but <24 hours
- **Stage 3**:
  - Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR
  - Urine output <0.3 ml/kg per hour for ≥24 hours OR
  - Anuria for >12 hours
  - [Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria]

Adverse Event (AE)

An adverse event is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs

	(including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device. **NOTE**: This definition includes events related to the investigational medical device or to the procedures involved but does not imply that there is a relationship between the adverse event and the device under investigation. *Pre-Existing Conditions:* Pre-existing medical conditions or a repeat of symptoms reported prior to the TAVR procedure will not be recorded as an AE. Pre-existing conditions that worsen during a study are to be considered adverse events. For users or other persons this classification is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE)	An adverse device effect is an adverse event related to the use of a medical device. This includes: • Any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device • Any event that is a result of a use error or intentional misuse
Anticipated Serious Adverse Device Effect (ASADE)	An anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).
As Treated (AT) Population	The AT population is defined by the treatment actually received, regardless of the assigned treatment. In the AT population, all subjects in whom vascular access in the contralateral femoral artery has been established for the intended deployment of the TriGuard HDH or TriGUARD *3* device will be assigned to the intervention group, and subjects in whom the TAVI procedure is initiated (but no vascular access for intended deployment of the TriGuard HDH or TriGUARD *3* is established) will be assigned to the control group.
Bleeding	Life-threatening or disabling bleeding:[35] • Fatal bleeding *(BARC type 5)* OR • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR

	• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units [Given that one *unit* of packed RBC typically will raise hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated] *(BARC type 3b)* Major bleeding *(BARC type 3a)*: • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND • Does not meet criteria of life-threatening or disabling bleeding Minor bleeding (BARC type 2 or 3a, depending on the severity): • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major
Cardiac tamponade	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure[35]
CCS (Canadian Cardiovascular Society) classification	Class I: Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina with strenuous, rapid, or prolonged exertion at work or recreation. Class II: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking up hill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress or during the first few hours after awakening may cause pain. Walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace and in normal conditions. Class III: Marked limitation of ordinary physical activity. Walking one-two blocks on a level and climbing one flight of stairs at normal pace results in angina. Class IV: Inability to carry on any physical activity without discomfort. Anginal syndrome may be present at rest.

Child-Pugh score

A scoring system used to assess the prognosis of chronic liver disease.[107] Scoring and interpretation as below:

Scoring			
Measure	**1 point**	**2 points**	**3 points**
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
Interpretation			
Points	**Class**	**One year survival**	**Two year survival**
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Clinical Frailty Scale

A measure of frailty based on clinical judgement, scored according to the following categories[108]:

1. **Very Fit** – People who are robust, active, energetic, and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. **Well** – People who have no active disease symptoms but are less fit than Category 1. Often, they exercise or are very active occasionally, e.g., seasonally.

3. **Managing Well** – People whose medical problems are well controlled, but are not regulatory active beyond routine walking.

4. **Vulnerable** – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being “slowed up,” and/or being tired during the day.

5. **Mildly Frail** – These people often have more evident slowing, and need help in high order independent activities of daily living (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation, and housework.

6. **Moderately Frail** – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing, and might need minimal assistance (cuing, standby) with dressing.

7. **Severely Frail** – Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~6 months).

8. **Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

	9. **Terminally Ill** – Approaching the end of life. The category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail. Based on the above categories, subjects also will be classified as Not Frail (Category 1-3), Mildly Frail (Category 4-5), and Moderately-to-Severely Frail (Category 6-9).
CNS hemorrhage	NeuroARC defined[3] as any brain, spinal cord, or retinal hemorrhage on the basis of imaging or pathology, not caused by trauma (includes symptomatic intracerebral hemorrhage [Type 1.b], symptomatic subarachnoid hemorrhage [Type 1.c], and covert CNS hemorrhage [Type 2.b])
CNS infarction	NeuroARC defined[3] as any brain, spinal cord, or retinal infarction on the basis of imaging, pathology, *or* clinical symptoms persisting for ≥24 h (includes ischemic stroke [Type 1.a], ischemic stroke with hemorrhagic conversion [Type 1.a.H], stroke not otherwise specified [Type 1.d], symptomatic hypoxic-ischemic injury [Type 1.e], covert CNS infarction [Type 2.a], and covert CNS infarction with hemorrhagic conversion [Type 2.a.H])
Cockcroft-Gault formula	A proxy for Glomerular Filtration Rate in which creatinine clearance is estimated from age, weight, and serum creatinine by the formula: $eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$ in which weight is recorded in kg and creatinine in mg/dL, and which is valid for male patients. If the patient is female, the result should be multiplied by 0.85.
Combined safety endpoint	Equivalent to the VARC-2 definition of “early safety (at 30 days)”,[1] defined as the composite of: • All-cause mortality • All stroke (disabling and non-disabling) • Life-threatening bleeding • Acute kidney injury – Stage 2 or 3 (including renal replacement therapy) • Coronary artery obstruction requiring intervention • Major vascular complication • Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
Covert CNS injury	Acutely asymptomatic brain or spinal cord injury detected by neuroimaging (NeuroARC Type 2), including[3]: <u>Type 2.a Covert CNS infarction</u>

Brain, spinal cord, or retinal cell death attributable to focal or multifocal ischemia, on the basis of neuroimaging or pathological evidence of CNS infarction, without a history of acute neurological symptoms consistent with the lesion location

Subtype 2.a.H Covert CNS infarction with hemorrhagic conversion

Covert CNS infarction includes hemorrhagic conversions. These should be subclassified as Class A or B when CNS infarction is the primary mechanism and neuroimaging or pathology confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 2.b Covert CNS hemorrhage

Neuroimaging or pathological evidence of CNS hemorrhage within the brain parenchyma, subarachnoid space, ventricular system, spinal cord, or retina on neuroimaging that is not caused by trauma, without a history of acute neurological symptoms consistent with the bleeding location

Device deployment time Time elapsed between insertion of the TriGuard HDH or TriGUARD *3* device into the groin access point and successful device deployment

Device deficiency Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunction, use error, and inadequate labeling. They may or may not affect device performance or lead to an adverse event.

Device interference Interaction of the TriGuard device with the TAVI system leading to:

- Inability to advance or manipulate the TAVI delivery system or valve prosthesis, OR
- Inability to deploy the TAVI valve prosthesis, OR
- Inability to retrieve the valve prosthesis or delivery system

Device malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use or protocol. NOTE: A device malfunction occurs when the device is used in compliance with the Instructions for Use, but does not perform as described in the Instructions for Use.
Device misuse	Any use of the investigational device by an investigator that is contradictory to the application described in the Instructions for Use will be categorized as device misuse. This is a form of Use Error.
Device positioning	Ability to position the TriGuard HDH or TriGUARD *3* device in the aortic arch to cover all major cerebral arteries, with proper positioning maintained (verified by fluoroscopy) until the following time points: o Final deployment of the first prosthetic valve o Final procedure (after any additional post-dilatation or additional valve implantations have been completed, and the TAVR delivery system has been removed) Extent of cerebral artery coverage will be reported as: o Complete (coverage of all 3 cerebral artery branches) o Partial (coverage of 1-2 cerebral artery branches) o None *Note:* Maintenance of device positioning to each time point and extent of cerebral coverage will be evaluated separately by the Angiographic Core Laboratory.
Efficacy Intention to Treat (eITT) population	The eITT analysis population is defined as: • Subjects who are enrolled in the trial and randomized to a treatment group, regardless of treatment actually received AND • Who do not have conversion to surgery or prolonged cardiac arrest (>3 minutes) prior to the post-procedure DW-MRI
Encephalopathy	Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.)
Evaluable	Evaluable subjects are those who are enrolled in the randomized portion of the trial (i.e., not Roll-In subjects)
General safety	Defined as the composite of the following adverse events (each VARC-2 defined): • All-cause mortality • All stroke (disabling and non-disabling)

	• Acute kidney injury – Stage 3 (including renal replacement therapy)
Hepatic failure	Child-Pugh Class C (see definition for classification scoring)
In-hospital procedural safety	The composite of the following Major Adverse Cardiovascular and Cerebrovascular events (MACCE): • All-cause mortality • All stroke (disabling and non-disabling) • Life threatening (or disabling) bleeding • Acute kidney injury – Stage 2 or 3 (including renal replacement therapy) • Major vascular complications
Intention to treat (ITT)	The principle of including outcomes of all subjects in the analysis who are randomized into the study, regardless of the treatment actually received. The ITT analysis population is defined as all subjects enrolled in the study, by assigned treatment, regardless of the treatment actually received.
Intracranial hemorrhage	Collection of blood between the brain and skull. Subcategorized as epidural, subdural, and subarachnoid bleeds.
Modification of Diet in Renal Disease (MDRD)	A proxy for Glomerular Filtration Rate in which creatinine clearance is estimated from age, serum creatinine, gender and race by the formula: GFR (mL/min/1.73 m2) = 175 × (Scr)-1.154 × (Age)-0.203 × (0.742 if female) × (1.212 if African American)
Modified RANKIN Score (mRS)	A commonly used scale for measuring stroke functional outcome.[109] See §16.5 for the standardized interview. The scale runs from 0 to 6. The scores and descriptions are: 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. Moderately 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

6. Dead

Montreal Cognitive Assessment (MoCA) worsening	A MoCA score decrease of 3 or more points from baseline to follow-up.
Mortality	**All-cause mortality[35]** **Cardiovascular mortality** Any of the following criteria: • Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause **Non-cardiovascular mortality** Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
Myocardial infarction (MI)	Peri-procedural MI (≤72 h after the index procedure):[35] • New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND • Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

	Spontaneous MI (>72 h after the index procedure). Any one of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: o Symptoms of ischemia o ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)] o New pathological Q waves in at least two contiguous leads o Imaging evidence of new loss of viable myocardium or new wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.
National Institute of Health Stroke Scale (NIHSS)	A commonly-used scale to assess stroke. See §16.6
Neurologic dysfunction without CNS injury	Acutely symptomatic (NeuroARC Type 3) without CNS injury, including:[3] Type 3.a TIA Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging) Type 3.b Delirium without CNS injury Transient nonfocal (global) neurological signs or symptoms (variable duration) without evidence of cell death by neuroimaging or pathology
Neurological events	See “stroke (VARC-2 defined)”, “Overt CNS Injury”, “Covert CNS Injury”, “Neurological dysfunction without CNS injury”, “CNS infarction”, and “CNS hemorrhage”

New neurologic impairment	NIHSS worsening at post-procedure (2-5 days post-procedure) accompanied by the presence of cerebral ischemic lesions.
NIHSS worsening	An NIHSS score increase from baseline to follow-up.
NYHA (New York Heart Association) functional capacity	Classified as[110]: Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Overt CNS Injury	Acutely symptomatic brain or spinal cord injury (NeuroARC Type 1), including[3]: Type 1.a Ischemic stroke Sudden onset of neurological signs or symptoms fitting a focal or multifocal vascular territory within the brain, spinal cord, or retina, that: 1) Persist for ≥24 h or until death, with pathology or neuroimaging evidence that demonstrates either: a) CNS infarction in the corresponding vascular territory (with or without hemorrhage); *or* b) Absence of other apparent causes (including hemorrhage), even if no evidence of acute ischemia in the corresponding vascular territory is detected *or* 2) Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory. *Note:* When CNS infarction location does not match the transient symptoms, the event would be classified as covert

CNS infarction (Type 2a) and a TIA (Type 3a), but not as an ischemic stroke.

Signs and symptoms consistent with stroke typically include an acute onset of 1 of the following: focal weakness and/or numbness; impaired language production or comprehension; homonymous hemianopia or quadrantanopsia; diplopia; altitudinal monocular blindness; hemispatial neglect; dysarthria; vertigo; or ataxia.

Subtype 1.a.H Ischemic stroke with hemorrhagic conversion

Ischemic stroke includes hemorrhagic conversions. These should be subclassified as Class A or B when ischemic stroke is the primary mechanism and pathology or neuroimaging confirms a hemorrhagic conversion.

Class A (Petechial hemorrhage): Petechiae or confluent petechiae within the infarction or its margins, but without a space-occupying effect

Class B (Confluent hemorrhage): Confluent hemorrhage or hematoma originating from within the infarcted area with space-occupying effect

Type 1.b Symptomatic intracerebral hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) caused by an intraparenchymal, intraventricular, spinal cord, or retinal collection of blood, not caused by trauma

Type 1.c Symptomatic subarachnoid hemorrhage

Rapidly developing neurological signs or symptoms (focal or global) and/or headache caused by bleeding into the subarachnoid space, not caused by trauma

Type 1.d Stroke, not otherwise specified

An episode of acute focal neurological signs or symptoms and/or headache presumed to be caused by CNS ischemia or CNS hemorrhage, persisting ≥24 h or until death, but without sufficient evidence to be classified as either (i.e., no neuroimaging performed)

Type 1.e Symptomatic hypoxic-ischemic injury

Nonfocal (global) neurological signs or symptoms due to diffuse brain, spinal cord, or retinal cell death (confirmed by pathology or neuroimaging) in a nonvascular distribution, attributable to hypotension and/or hypoxia

Per Treatment (PT) population

The PT population is defined as subjects in the Intervention group in whom device positioning is maintained until final

	procedure with complete cerebral coverage, and all Control group subjects.
Procedure success	Technical success in the absence of any investigational device-related or investigational procedure-related in-hospital procedural safety events.

Prosthetic Valve Dysfunction

Defined according to VARC criteria in the table below:[35]

Prosthetic Valve Dysfunction

Prosthetic aortic valve stenosis*			
	Normal	Mild Stenosis	Moderate/Severe Stenosis
Quantitative Parameters (Flow-dependent)†			
Peak velocity	<3 m/s	3-4 m/s	>4 m/s
Mean gradient	<20 mmHg	20-40 mmHg	>40 mmHg
Quantitative Parameters (Flow-independent)			
Doppler velocity index‡	>0.35	0.35-0.25	<0.25
Effective orifice area¶	>1.1 cm^2	1.1-0.8 cm^2	<0.8 cm^2
Effective orifice area§	>0.9 cm^2	0.9-0.6 cm^2	<0.6 cm^2
Prosthesis-patient mismatch (PPM)			
	Insignificant	Moderate	Severe
Indexed effective orifice area**	>0.85 cm^2/m^2	0.85-0.65 cm^2/m^2	<0.65 cm^2/m^2
Indexed effective orifice area††	>0.70 cm^2/m^2	0.90-0.60 cm^2/m^2	<0.60 cm^2/m^2
Prosthetic aortic valve regurgitation			
	Mild	Moderate	Severe
Semi-quantitative Parameters			
Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)¶¶	<10	10-29	≥30
Quantitative Parameters‡			
Regurgitant volume (ml/beat)	<30	30-59	≥60
Regurgitant fraction (%)	<30	30-49	≥50
EROA (cm^2)	0.10	0.10-0.29	≥0.30

*In conditions of normal or near normal stroke volume (50–70 mL)
†These parameters are more affected by flow, including concomitant aortic regurgitation
‡For LVOT >2.5 cm, significant stenosis criteria is <0.20
¶Use in setting of BSA ≥1.6 cm^2 (note: dependent on the size of the valve and the size of the native annulus)
§Use in setting of BSA <1.6 cm^2
**Use in setting of BMI <30 kg/cm^2
††Use in setting of BMI ≥30 kg/cm^2
¶¶Not well-validated and may overestimate severity compared to quantitative Doppler

Serious Adverse Device Effect (SADE)

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)

A serious adverse event is an adverse event that:

1. Led to a death
2. Led to a serious deterioration in the health of the subject that:
    a. Resulted in a life-threatening illness or injury
    b. Resulted in a permanent impairment of a body structure or a body function
    c. Required in-patient hospitalization or prolongation of existing hospitalization
    d. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Stroke (VARC-2 defined)

Diagnostic criteria:

- Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Stroke: duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
- TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist (Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies [CT scan or brain MRI]).
- Confirmation of the diagnosis by at least one of the following:
    - Neurologist or neurosurgical specialist

- Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke classification:

- Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue
- Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
- A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic

Stroke definitions (Modified Rankin Scale assessments should be made by qualified individuals according to a certification process):

- Disabling stroke – a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline
- Non-disabling stroke – a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline

Successful device deployment

Ability to access the aortic arch with the TriGuard HDH or TriGUARD *3* delivery catheter and deploy the device from the delivery catheter into the aortic arch.

Successful device retrieval

Ability to retrieve the TriGuard device and remove the TriGuard CEPD.

TAVI device success

Equivalent to the VARC definition[111] of "device success" for transcatheter aortic valves. Defined as:

- Absence of procedural mortality AND
- Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
- Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (VARC-defined) and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation (VARC-defined)

Technical success

Successful TriGuard HDH or TriGUARD *3* device deployment, device positioning, and successful device retrieval in the absence of device interference

Total procedural time	Time elapsed between first arterial access and removal of the last catheter from the arterial access sheath
Unanticipated Adverse Device Effect (UADE)	An unanticipated adverse device effect is any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects. NOTE: An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the investigational plan or application (including a supplementary plan or application).
Use Error	Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user. NOTE 1: Use error includes slips, lapses and mistakes. NOTE 2: An unexpected physiological response of the patient does not itself constitute a use error.
Vascular access site and access-related complications	Major Vascular Complications:[35] • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR

- Permanent access site-related nerve injury

Minor vascular complications:

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding, visceral ischemia or neurological impairment OR
- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

16.2 Appendix II: Acronyms

AE	adverse event
ADE	adverse device effect
AF	atrial fibrillation
ALT/SGPT	alanine transaminase / serum glutamic pyruvic transaminase
AKI	acute kidney injury
AMI	acute myocardial infarction
ANOVA	analysis of variance
AS	aortic stenosis
ASA	acetylsalicylic acid
ASADE	anticipated serious adverse device effect
AST/SGOT	Aspartate transaminase / serum glutamic oxaloacetic transaminase
AT	As treated
BARC	Bleeding Academic Research Consortium
BAV	balloon aortic valvuloplasty
BUN	blood urea nitrogen
CABG	coronary artery bypass graft surgery
CCS	Canadian Cardiovascular Society
CEC	clinical events committee
CEPD	Cerebral Embolic Protection Device
CI	confidence interval
CIP	clinical investigation plan
CK	creatine kinase
CK-MB	creatine kinase-MB fraction
CNS	central nervous system
CRF	case report form

CT	computed tomography
DAPT	dual antiplatelet therapy
DICOM	Digital Imaging and Communications in Medicine
DSMB	data and safety monitoring Board (Interchangeable with DSMC)
DW-MRI	diffusion-weighted magnetic resonance imaging
EC	Ethics Committee
ECG	electrocardiogram
EDC	electronic data capture (system)
EDD/EPD	embolic deflection device/embolic protection device (see also CEPD)
eGFR	estimated Glomerular Filtration Rate
eITT	efficacy Intention to Treat
EU	European Union
F	french (catheter scale system)
FDA	U.S. Food and Drug Administration
GCP	good clinical practices
GI	gastrointestinal
ICH	International Conference on Harmonization
INR	international normalized ratio
IQR	interquartile range
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	intention to treat
IV	intravenous
LAO	left anterior oblique
LBBB	left bundle branch block

LV	left ventricle/left ventricular
MACCE	major adverse cardiovascular and cerebrovascular events
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NeuroARC	Neurologic Academic Research Consortium
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OPC	objective performance criterion
PCI	percutaneous coronary intervention
PP	per protocol
PPM	prosthesis-patient mismatch
PT	per treatment
PTT	partial thromboplastin time
QD	*quaque die* (daily)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	red blood cells
RI	roll-in
SADE	serious adverse device effect
SAE	serious adverse event
SAVR	surgical aortic valve replacement
SD	standard deviation
SF-36	Short Form 36 Health Survey
SOC	standard of care

STS	Society of Thoracic Surgeons
TAVI	transcatheter aortic valve implantation
TEE	transesophageal echocardiography
TIA	transient ischemic attack
UADE	unanticipated adverse device effect
URL	upper reference limit
US	United States
VARC	Valve Academic Research Consortium
WBC	white blood cell

16.3 Appendix III: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

a. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

b. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote

c. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote

d. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

e. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note: **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

16.4 Appendix IV: References

1. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW and Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg*. 2013;145:6-23.
2. Finkelstein DM and Schoenfeld DA. Combining mortality and longitudinal measures in clinical trials. *Statistics in medicine*. 1999;18:1341-54.
3. Lansky AJ, Messé SR, Brickman AM, Dwyer MG, van der Worp HB, Lazar RM, Pietras CG, Abrams KJ, McFadden E, Petersen NH, Browndyke JN, Prendergast B, Ng VG, Cutlip DE, Kapadia S, Krucoff MW, Linke A, Moy CS, Schofer J, van Es GA, Virmani R, Popma JJ, Parides MK, Kodali S, Bilello M, Zivadinov R, Akar J, Furie KL, Gress D, Voros S, Moses J, Greer D, Forrest JK, Holmes D, Kappetein AP, Mack M and Baumbach A. Proposed standardized neurological endpoints for cardiovascular clinical trials: an Academic Research Consortium initiative. *J Am Coll Cardiol*. 2017;(in press).
4. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D and Pocock SJ. Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients. *N Engl J Med*. 2011;364:2187-98.
5. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D and Pocock S. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *New England Journal of Medicine*. 2010;363:1597-607.
6. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J, Jr., Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S and Oh JK. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-8.
7. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J, Jr., Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S and Oh JK. Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery. *J Am Coll Cardiol*. 2014;63:1972-81.
8. Lansky AJ, Schofer J, Tchetche D, Stella P, Pietras CG, Parise H, Abrams K, Forrest JK, Cleman M, Reinohl J, Cuisset T, Blackman D, Bolotin G, Spitzer S, Kappert U, Gilard M, Modine T, Hildick-Smith D, Haude M, Margolis P, Brickman AM, Voros S and Baumbach A. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J*. 2015;36:2070-2078.
9. Kapadia SR, Kodali S, Makkar R, Mehran R, Lazar RM, Zivadinov R, Dwyer MG, Jilaihawi H, Virmani R, Anwaruddin S, Thourani VH, Nazif T, Mangner N, Woitek F, Krishnaswamy A, Mick S, Chakravarty T, Nakamura M, McCabe JM, Satler L, Zajarias A, Szeto WY, Svensson L, Alu MC, White RM, Kraemer C, Parhizgar A, Leon MB and Linke A. Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement. *Journal of the American College of Cardiology*. 2017;69:367-377.
10. Chen YH, DeMets DL and Lan KK. Increasing the sample size when the unblinded interim result is promising. *Stat Med*. 2004;23:1023-38.
11. Mehta CR and Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Stat Med*. 2011;30:3267-84.
12. McKhann GM, Grega MA, Borowicz LM, Jr., Baumgartner WA and Selnes OA. Stroke and encephalopathy after cardiac surgery: an update. *Stroke*. 2006;37:562-71.

13. Nuis RJ, Piazza N, Van Mieghem NM, Otten AM, Tzikas A, Schultz CJ, van der Boon R, van Geuns RJ, van Domburg RT, Koudstaal PJ, Kappetein AP, Serruys PW and de Jaegere PP. In-hospital complications after transcatheter aortic valve implantation revisited according to the valve academic research consortium definitions. *Catheter Cardiovasc Interv*. 2011.
14. Selim M. Perioperative stroke. *N Engl J Med*. 2007;356:706-13.
15. Fuchs S, Stabile E, Kinnaird TD, Mintz GS, Gruberg L, Canos DA, Pinnow EE, Kornowski R, Suddath WO, Satler LF, Pichard AD, Kent KM and Weissman NJ. Stroke complicating percutaneous coronary interventions: incidence, predictors, and prognostic implications. *Circulation*. 2002;106:86-91.
16. Dukkipati S, O'Neill WW, Harjai KJ, Sanders WP, Deo D, Boura JA, Bartholomew BA, Yerkey MW, Sadeghi HM and Kahn JK. Characteristics of cerebrovascular accidents after percutaneous coronary interventions. *J Am Coll Cardiol*. 2004;43:1161-7.
17. Aggarwal A, Dai D, Rumsfeld JS, Klein LW and Roe MT. Incidence and predictors of stroke associated with percutaneous coronary intervention. *Am J Cardiol*. 2009;104:349-53.
18. Segal AZ, Abernethy WB, Palacios IF, BeLue R and Rordorf G. Stroke as a complication of cardiac catheterization: risk factors and clinical features. *Neurology*. 2001;56:975-7.
19. Omran H, Schmidt H, Hackenbroch M, Illien S, Bernhardt P, von der Recke G, Fimmers R, Flacke S, Layer G, Pohl C, Luderitz B, Schild H and Sommer T. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet*. 2003;361:1241-6.
20. Rodes-Cabau J, Dumont E, Boone RH, Larose E, Bagur R, Gurvitch R, Bedard F, Doyle D, De Larochelliere R, Jayasuria C, Villeneuve J, Marrero A, Cote M, Pibarot P and Webb JG. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. *J Am Coll Cardiol*. 2011;57:18-28.
21. Stortecky S, Buellesfeld L, Wenaweser P, Heg D, Pilgrim T, Khattab AA, Gloekler S, Huber C, Nietlispach F, Meier B, Juni P and Windecker S. Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2013;6:77-84.
22. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC and Webb JG. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *New England Journal of Medicine*. 2016;374:1609-1620.
23. Eggebrecht H, Schmermund A, Voigtlander T, Kahlert P, Erbel R and Mehta RH. Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients. *EuroIntervention*. 2012;8:129-38.
24. Miller DC, Blackstone EH, Mack MJ, Svensson LG, Kodali SK, Kapadia S, Rajeswaran J, Anderson WN, Moses JW, Tuzcu EM, Webb JG, Leon MB and Smith CR. Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: Occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. *J Thorac Cardiovasc Surg*. 2012;143:832-843 e13.
25. Hamon M, Baron JC and Viader F. Periprocedural stroke and cardiac catheterization. *Circulation*. 2008;118:678-83.
26. Osranek M, Pilip A, Patel PR, Molisse T, Tunick PA and Kronzon I. Amounts of aortic atherosclerosis in patients with aortic stenosis as determined by transesophageal echocardiography. *Am J Cardiol*. 2009;103:713-7.
27. Kahlert P, Al-Rashid F, Doettger P, Mori K, Plicht B, Wendt D, Bergmann L, Kottenberg E, Schlamann M, Mummel P, Holle D, Thielmann M, Jakob HG, Konorza T, Heusch G, Erbel R and Eggebrecht H. Cerebral Embolization During Transcatheter Aortic Valve Implantation: A Transcranial Doppler Study. *Circulation*. 2012.
28. Kahlert P, Al-Rashid F, Plicht B, Hildebrandt H, Patsalis P, Chilali K, Wendt D, Thielmann M, Bergmann L, Kottenberg E, Schlamann M, Eggebrecht H, Jakob H, Heusch G, Konorza T and Erbel R. Incidence, predictors, origin and prevention of early and late neurological events after

transcatheter aortic valve implantation (TAVI): a comprehensive review of current data. *Journal of thrombosis and thrombolysis*. 2013;35:436-449.
29. Hauville C, Ben-Dor I, Lindsay J, Pichard AD and Waksman R. Clinical and silent stroke following aortic valve surgery and transcatheter aortic valve implantation. *Cardiovascular revascularization medicine : including molecular interventions*. 2012.
30. Hynes BG and Rodes-Cabau J. Transcatheter aortic valve implantation and cerebrovascular events: the current state of the art. *Annals of the New York Academy of Sciences*. 2012;1254:151-63.
31. Bendszus M and Stoll G. Silent cerebral ischaemia: hidden fingerprints of invasive medical procedures. *Lancet Neurol*. 2006;5:364-72.
32. Vermeer SE, Longstreth WT, Jr. and Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol*. 2007;6:611-9.
33. Mullins ME, Schaefer PW, Sorensen AG, Halpern EF, Ay H, He J, Koroshetz WJ and Gonzalez RG. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. *Radiology*. 2002;224:353-60.
34. Cooper HA, Thompson EC, Laureno R, Fuisz A, Mark AS, Lin M and Goldstein SA. Subclinical brain embolization in left-sided infective endocarditis: results from the evaluation by MRI of the brains of patients with left-sided intracardiac solid masses (EMBOLISM) pilot study. *Circulation*. 2009;120:585-91.
35. Kappetein AP, Head SJ, Genereux P, Piazza N, Van Mieghem N, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, Van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack M, Mehran R, Rodes-Cabau J, Vranckx P, Webb J, Windecker S, Serruys P and Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve replacement: the VARC-2 consensus document. *J Am Coll Cardiol (In Press)*. 2012.
36. Arnold M, Schulz-Heise S, Achenbach S, Ott S, Dorfler A, Ropers D, Feyrer R, Einhaus F, Loders S, Mahmoud F, Roerick O, Daniel WG, Weyand M, Ensminger SM and Ludwig J. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. *JACC Cardiovasc Interv*. 2010;3:1126-32.
37. Astarci P, Price J, Glineur D, D'Hoore W, Kefer J, Elkhoury G, Grandin C and Vanoverschelde JL. Cerebral embolization during percutaneous valve implantation does not occur during balloon inflation valvuloplasty: prospective diffusion-weighted brain MRI study. *J Heart Valve Dis*. 2013;22:79-84.
38. Fairbairn TA, Mather AN, Bijsterveld P, Worthy G, Currie S, Goddard AJ, Blackman DJ, Plein S and Greenwood JP. Diffusion-weighted MRI determined cerebral embolic infarction following transcatheter aortic valve implantation: assessment of predictive risk factors and the relationship to subsequent health status. *Heart*. 2012;98:18-23.
39. Ghanem A, Muller A, Sinning JM, Kocurek J, Becker BV, Vogel M, Vasa-Nicotera M, Hammerstingl C, Schwab JO, Nahle CP, Thomas D, Wagner M, Grube E, Werner N and Nickenig G. Prognostic value of cerebral injury following transfemoral aortic valve implantation. *EuroIntervention*. 2013;8:1296-306.
40. Kahlert P, Knipp SC, Schlamann M, Thielmann M, Al-Rashid F, Weber M, Johansson U, Wendt D, Jakob HG, Forsting M, Sack S, Erbel R and Eggebrecht H. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation*. 2010;121:870-8.
41. Knipp SC, Kahlert P, Jokisch D, Schlamann M, Wendt D, Weimar C, Jakob H and Thielmann M. Cognitive function after transapical aortic valve implantation: a single-centre study with 3-month follow-up. *Interact Cardiovasc Thorac Surg*. 2013;16:116-22.
42. Uddin A, Fairbairn TA, Djoukhader I, Currie S, Steadman CD, Motwani M, Kidambi A, Goddard A, Blackman D, McCann GP, Plein S and Greenwood JP. Difference between cerebral embolic events following Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR): a Diffusion weighted MRI study. *Journal of Cardiovascular Magnetic Resonance*. 2013;15(Suppl 1).
43. Ghanem A, Muller A, Nahle CP, Kocurek J, Werner N, Hammerstingl C, Schild HH, Schwab JO, Mellert F, Fimmers R, Nickenig G and Thomas D. Risk and fate of cerebral embolism after

transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. *J Am Coll Cardiol*. 2010;55:1427-32.
44. Onsea K, Agostoni P, Samim M, Voskuil M, Kluin J, Budde R, Hendrikse J, Ramjankhan F, van Klarenbosch J, Doesburg P, Sieswerda G and Stella P. First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. *EuroIntervention*. 2012;8:51-6.
45. Vermeer SE, Prins ND, den Heijer T, Hofman A, Koudstaal PJ and Breteler MM. Silent brain infarcts and the risk of dementia and cognitive decline. *N Engl J Med*. 2003;348:1215-22.
46. Miwa K, Hoshi T, Hougaku H, Tanaka M, Furukado S, Abe Y, Okazaki S, Sakaguchi M, Sakoda S and Kitagawa K. Silent cerebral infarction is associated with incident stroke and TIA independent of carotid intima-media thickness. *Internal medicine (Tokyo, Japan)*. 2010;49:817-22.
47. Barber PA, Hach S, Tippett LJ, Ross L, Merry AF and Milsom P. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. *Stroke*. 2008;39:1427-33.
48. Knipp SC, Matatko N, Schlamann M, Wilhelm H, Thielmann M, Forsting M, Diener HC and Jakob H. Small ischemic brain lesions after cardiac valve replacement detected by diffusion-weighted magnetic resonance imaging: relation to neurocognitive function. *Eur J Cardiothorac Surg*. 2005;28:88-96.
49. Stolz E, Gerriets T, Kluge A, Klovekorn WP, Kaps M and Bachmann G. Diffusion-weighted magnetic resonance imaging and neurobiochemical markers after aortic valve replacement: implications for future neuroprotective trials? *Stroke*. 2004;35:888-92.
50. Astarci P, Glineur D, Kefer J, D'Hoore W, Renkin J, Vanoverschelde JL, El Khoury G and Grandin C. Magnetic resonance imaging evaluation of cerebral embolization during percutaneous aortic valve implantation: comparison of transfemoral and trans-apical approaches using Edwards Sapiens valve. *Eur J Cardiothorac Surg*. 2011.
51. Drews T, Pasic M, Buz S, Unbehaun A, Dreysse S, Kukucka M, Mladenow A and Hetzer R. Transcranial Doppler Sound Detection of Cerebral Microembolism during Transapical Aortic Valve Implantation. *Thorac Cardiovasc Surg*. 2011;59:237-42.
52. Knipp SC. C2-2 Cerebral ischemia and cognitive functioning after transapical minimally invasive aortic valve implantation. Paper presented at: European Society for Cardiovascular and Endovascular Surgery (ESCVS) International Congress; 2011; Moscow, Russia.
53. Russell D. Cerebral microemboli and cognitive impairment. *J Neurol Sci*. 2002;203-204:211-4.
54. Duffis EJ, Jones D, Tighe D and Moonis M. Neurological complications of coronary angiographic procedures. *Expert Rev Cardiovasc Ther*. 2007;5:1113-21.
55. Fearn SJ, Pole R, Wesnes K, Faragher EB, Hooper TL and McCollum CN. Cerebral injury during cardiopulmonary bypass: emboli impair memory. *J Thorac Cardiovasc Surg*. 2001;121:1150-60.
56. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J and Saver JL. Diffusion MRI in patients with transient ischemic attacks. *Stroke*. 1999;30:1174-80.
57. Choi SH, Na DL, Chung CS, Lee KH, Na DG and Adair JC. Diffusion-weighted MRI in vascular dementia. *Neurology*. 2000;54:83-9.
58. Cumming TB, Bernhardt J and Linden T. The montreal cognitive assessment: short cognitive evaluation in a large stroke trial. *Stroke*. 2011;42:2642-4.
59. Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R and Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke*. 1989;20:864-870.
60. Tissue Plasminogen Activator for Acute Ischemic Stroke. *New England Journal of Medicine*. 1995;333:1581-1588.
61. Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, Woolson RF and Hansen MD. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53:126-31.
62. Chang KC, Tseng MC, Weng HH, Lin YH, Liou CW and Tan TY. Prediction of length of stay of first-ever ischemic stroke. *Stroke*. 2002;33:2670-4.
63. Schlegel D, Kolb SJ, Luciano JM, Tovar JM, Cucchiara BL, Liebeskind DS and Kasner SE. Utility of the NIH Stroke Scale as a predictor of hospital disposition. *Stroke*. 2003;34:134-7.

64. Siegler JE, Boehme AK, Kumar AD, Gillette MA, Albright KC and Martin-Schild S. What Change in the National Institutes of Health Stroke Scale Should Define Neurologic Deterioration in Acute Ischemic Stroke? *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association*. 2013;22:675-682.
65. DeGraba TJ, Hallenbeck JM, Pettigrew KD, Dutka AJ and Kelly BJ. Progression in acute stroke: value of the initial NIH stroke scale score on patient stratification in future trials. *Stroke*. 1999;30:1208-12.
66. Patel SC, Levine SR, Tilley BC and et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *Jama*. 2001;286:2830-2838.
67. Johnston SC, Leira EC, Hansen MD and Adams HP, Jr. Early recovery after cerebral ischemia risk of subsequent neurological deterioration. *Annals of neurology*. 2003;54:439-44.
68. Aslanyan S, Weir CJ, Johnston SC and Lees KR. Poststroke neurological improvement within 7 days is associated with subsequent deterioration. *Stroke*. 2004;35:2165-70.
69. Kwan J and Hand P. Early neurological deterioration in acute stroke: clinical characteristics and impact on outcome. *QJM : monthly journal of the Association of Physicians*. 2006;99:625-33.
70. Roquer J, Rodriguez-Campello A, Gomis M, Jimenez-Conde J, Cuadrado-Godia E, Vivanco R, Giralt E, Sepulveda M, Pont-Sunyer C, Cucurella G and Ois A. Acute stroke unit care and early neurological deterioration in ischemic stroke. *Journal of neurology*. 2008;255:1012-7.
71. Toyoda K, Fujimoto S, Kamouchi M, Iida M and Okada Y. Acute Blood Pressure Levels and Neurological Deterioration in Different Subtypes of Ischemic Stroke. *Stroke*. 2009;40:2585-2588.
72. Wendt D, Kleinbongard P, Knipp S, Al-Rashid F, Gedik N, El Chilali K, Schweter S, Schlamann M, Kahlert P, Neuhauser M, Forsting M, Erbel R, Heusch G, Jakob H and Thielmann M. Intraaortic Protection From Embolization in Patients Undergoing Transaortic Transcatheter Aortic Valve Implantation. *Ann Thorac Surg*. 2015;100:686-91.
73. Van Mieghem NM, van Gils L, Ahmad H, van Kesteren F, van der Werf HW, Brueren G, Storm M, Lenzen M, Daemen J, van den Heuvel AF, Tonino P, Baan J, Koudstaal PJ, Schipper ME, van der Lugt A and de Jaegere PP. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. *EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology*. 2016;12:499-507.
74. Haussig S, Mangner N, Dwyer MG, Lehmkuhl L, Lucke C, Woitek F, Holzhey DM, Mohr FW, Gutberlet M, Zivadinov R, Schuler G and Linke A. Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial. *Jama*. 2016;316:592-601.
75. Lansky AJ. The Keystone Deflector Device: Updates from the DEFLECT I Trial. Paper presented at: Transcatheter Cardiovascular Therapeutics; 2013; San Francisco, CA, USA.
76. Bob-Manuel T, Sharma A, Nanda A, Ardeshna D, Skelton WP and Khouzam RN. A review of racial disparities in transcatheter aortic valve replacement (TAVR): accessibility, referrals and implantation. *Annals of Translational Medicine*. 2018;6.
77. Pocock SJ, Ariti CA, Collier TJ and Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. *Eur Heart J*. 2012;33:176-82.
78. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJ, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S and Serruys PW. Standardized endpoint definitions for Transcatheter Aortic Valve Implantation clinical trials: a consensus report from the Valve Academic Research Consortium. *Journal of the American College of Cardiology*. 2011;57:253-69.
79. Abdel-Wahab M, Mostafa AE, Geist V, Stocker B, Gordian K, Merten C, Richardt D, Toelg R and Richardt G. Comparison of outcomes in patients having isolated transcatheter aortic valve implantation versus combined with preprocedural percutaneous coronary intervention. *Am J Cardiol*. 2012;109:581-6.
80. Buchanan GL, Chieffo A, Montorfano M, Maisano F, Latib A, Godino C, Cioni M, Gullace MA, Franco A, Gerli C, Alfieri O and Colombo A. The role of sex on VARC outcomes following transcatheter aortic valve implantation with both Edwards SAPIEN and Medtronic CoreValve ReValving System(R) devices: the Milan registry. *EuroIntervention*. 2011;7:556-63.

81. D'Ascenzo F, Gonella A, Moretti C, Omede P, Salizzoni S, La Torre M, Giordana F, Barbanti M, Ussia GP, Brambilla N, Bedogni F, Gaita F, Tamburino C and Sheiban I. Gender differences in patients undergoing TAVI: a multicentre study. *EuroIntervention*. 2013;9:367-72.
82. Dubois C, Coosemans M, Rega F, Poortmans G, Belmans A, Adriaenssens T, Herregods MC, Goetschalckx K, Desmet W, Janssens S, Meyns B and Herijgers P. Prospective evaluation of clinical outcomes in all-comer high-risk patients with aortic valve stenosis undergoing medical treatment, transcatheter or surgical aortic valve implantation following heart team assessment. *Interact Cardiovasc Thorac Surg*. 2013;17:492-500.
83. van der Boon RM, Marcheix B, Tchetche D, Chieffo A, Van Mieghem NM, Dumonteil N, Vahdat O, Maisano F, Serruys PW, Kappetein AP, Fajadet J, Colombo A, Carrie D, van Domburg RT and de Jaegere PP. Transapical versus transfemoral aortic valve implantation: a multicenter collaborative study. *Ann Thorac Surg*. 2014;97:22-8.
84. Eltchaninoff H, Durand E, Borz B, Godin M, Tron C, Litzler PY, Bessou JP, Bejar K, Fraccaro C, Sanchez-Giron C, Dacher JN, Bauer F and Cribier A. Prospective analysis of 30-day safety and performance of transfemoral transcatheter aortic valve implantation with Edwards SAPIEN XT versus SAPIEN prostheses. *Arch Cardiovasc Dis*. 2012;105:132-40.
85. Gurvitch R, Toggweiler S, Willson AB, Wijesinghe N, Cheung A, Wood DA, Ye J and Webb JG. Outcomes and complications of transcatheter aortic valve replacement using a balloon expandable valve according to the Valve Academic Research Consortium (VARC) guidelines. *EuroIntervention*. 2011;7:41-8.
86. Hammerer M, Schuler J, Altenberger J, Kraus J, Prinz E, Matzinger M, Pichler M and Heigert M. Rehospitalization rates after transcatheter aortic valve implantation. *Wiener klinische Wochenschrift*. 2012;124:45-52.
87. Hayashida K, Morice MC, Chevalier B, Hovasse T, Romano M, Garot P, Farge A, Donzeau-Gouge P, Bouvier E, Cormier B and Lefevre T. Sex-related differences in clinical presentation and outcome of transcatheter aortic valve implantation for severe aortic stenosis. *J Am Coll Cardiol*. 2012;59:566-71.
88. van der Boon RM, Nuis RJ, Benitez LM, Van Mieghem NM, Perez S, Cruz L, van Geuns RJ, Serruys PW, van Domburg RT, Dager AE and de Jaegere PP. Frequency, determinants and prognostic implications of infectious complications after transcatheter aortic valve implantation. *Am J Cardiol*. 2013;112:104-10.
89. Scherner M, Madershahian N, Rosenkranz S, Slottosch I, Kuhn E, Langebartels G, Deppe A, Wippermann J, Choi YH, Strauch JT and Wahlers T. Transapical aortic valve implantation: experiences and survival analysis up to three years. *J Card Surg*. 2012;27:653-61.
90. Seiffert M, Schnabel R, Conradi L, Diemert P, Schirmer J, Koschyk D, Linder M, Kersten JF, Grosser A, Wilde S, Blankenberg S, Reichenspurner H, Baldus S and Treede H. Predictors and outcomes after transcatheter aortic valve implantation using different approaches according to the valve academic research consortium definitions. *Catheter Cardiovasc Interv*. 2013;82:640-52.
91. Stahli BE, Bunzli R, Grunenfelder J, Buhler I, Felix C, Bettex D, Biaggi P, Tanner FC, Nguyen-Kim DL, Plass A, Ge H, Falk V, Luscher TF, Corti R, Maier W and Altwegg LA. Transcatheter aortic valve implantation (TAVI) outcome according to standardized endpoint definitions by the Valve Academic Research Consortium (VARC). *J Invasive Cardiol*. 2011;23:307-12.
92. Ussia GP, Barbanti M, Petronio AS, Tarantini G, Ettori F, Colombo A, Violini R, Ramondo A, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, De Carlo M, Napodano M, Fiorina C, De Marco F, Antoniucci D, de Cillis E, Capodanno D and Tamburino C. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. *Eur Heart J*. 2012.
93. Wenaweser P, Pilgrim T, Guerios E, Stortecky S, Huber C, Khattab AA, Kadner A, Buellesfeld L, Gloekler S, Meier B, Carrel T and Windecker S. Impact of coronary artery disease and percutaneous coronary intervention on outcomes in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. *EuroIntervention*. 2011;7:541-8.
94. Yamamoto M, Hayashida K, Mouillet G, Chevalier B, Meguro K, Watanabe Y, Dubois-Rande JL, Morice MC, Lefevre T and Teiger E. Renal function-based contrast dosing predicts acute kidney injury following transcatheter aortic valve implantation. *JACC Cardiovasc Interv*. 2013;6:479-86.

95. Abramowitz Y, Banai S, Katz G, Steinvil A, Arbel Y, Havakuk O, Halkin A, Ben-Gal Y, Keren G and Finkelstein A. Comparison of early and late outcomes of TAVI alone compared to TAVI plus PCI in aortic stenosis patients with and without coronary artery disease. *Catheter Cardiovasc Interv*. 2014;83:649-54.
96. Greif M, Lange P, Nabauer M, Schwarz F, Becker C, Schmitz C, Pohl T, D'Anastasi M, Boekstegers P, Massberg S and Kupatt C. Transcutaneous aortic valve replacement with the Edwards SAPIEN XT and Medtronic CoreValve prosthesis under fluoroscopic guidance and local anaesthesia only. *Heart*. 2014;100:691-5.
97. Sabate M, Canovas S, Garcia E, Hernandez Antolin R, Maroto L, Hernandez JM, Alonso Briales JH, Munoz Garcia AJ, Gutierrez-Ibanes E and Rodriguez-Roda J. In-hospital and Mid-term Predictors of Mortality After Transcatheter Aortic Valve Implantation: Data From the TAVI National Registry 2010-2011. *Revista espanola de cardiologia (English ed)*. 2013;66:949-58.
98. D'Onofrio A, Salizzoni S, Agrifoglio M, Cota L, Luzi G, Tartara PM, Cresce GD, Aiello M, Savini C, Cassese M, Cerillo A, Punta G, Cioni M, Gabbieri D, Zanchettin C, Agostinelli A, Mazzaro E, Di Gregorio O, Gatti G, Faggian G, Filippini C, Rinaldi M and Gerosa G. Medium term outcomes of transapical aortic valve implantation: results from the italian registry of trans-apical aortic valve implantation. *Ann Thorac Surg*. 2013;96:830-6.
99. Tarantini G, Gasparetto V, Napodano M, Frigo AC, Fraccaro C, Buja P, D'Onofrio A, D'Amico G, Barioli A, Baritussio A, Facchin M, Dariol G, Isabella G, Gerosa G and Iliceto S. Transcatheter aortic valve implantation and bleeding: Focus on Valve Academic Research Consortium-2 classification. *Int J Cardiol*. 2013.
100. Chopard R, Meneveau N, Chocron S, Gilard M, Laskar M, Eltchaninoff H, Iung B, Leprince P, Teiger E, Chevreul K, Prat A, Lievre M, Leguerrier A, Donzeau-Gouge P, Fajadet J and Schiele F. Impact of chronic obstructive pulmonary disease on Valve Academic Research Consortium-defined outcomes after transcatheter aortic valve implantation (from the FRANCE 2 Registry). *Am J Cardiol*. 2014;113:1543-9.
101. Conradi L, Seiffert M, Schirmer J, Koschyk D, Blankenberg S, Reichenspurner H, Diemert P and Treede H. Transapical transcatheter aortic valve implantation without prior balloon aortic valvuloplasty: feasible and safe. *Eur J Cardiothorac Surg*. 2013.
102. Magri CJ, Chieffo A, Durante A, Latib A, Montorfano M, Maisano F, Cioni M, Agricola E, Covello RD, Gerli C, Franco A, Spagnolo P, Alfieri O and Colombo A. Impact of mean platelet volume on combined safety endpoint and vascular and bleeding complications following percutaneous transfemoral transcatheter aortic valve implantation. *BioMed research international*. 2013;2013:645265.
103. Seco M, Martinez G, Bannon PG, Cartwright BL, Adams M, Ng M, Wilson MK and Vallely MP. Transapical aortic valve implantation-an Australian experience. *Heart Lung Circ*. 2014;23:462-8.
104. Giustino G, Sorrentino S, Mehran R, Faggioni M and Dangas G. Cerebral Embolic Protection During TAVR: A Clinical Event Meta-Analysis. *Journal of the American College of Cardiology*. 2017;69:465-466.
105. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, Thourani VH, Babaliaros VC, Webb JG, Herrmann HC, Bavaria JE, Kodali S, Brown DL, Bowers B, Dewey TM, Svensson LG, Tuzcu M, Moses JW, Williams MR, Siegel RJ, Akin JJ, Anderson WN, Pocock S, Smith CR and Leon MB. Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis. *New England Journal of Medicine*. 2012;366:1696-1704.
106. Siontis GC, Juni P, Pilgrim T, Stortecky S, Bullesfeld L, Meier B, Wenaweser P and Windecker S. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. *J Am Coll Cardiol*. 2014;64:129-40.
107. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC and Williams R. Transection of the oesophagus for bleeding oesophageal varices. *The British journal of surgery*. 1973;60:646-9.
108. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I and Mitnitski A. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2005;173:489-95.
109. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ and van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-7.

110. The Criteria Committee of the New York Heart Association. *Nomenclature and criteria for diagnosis of diseases of the heart and great vessels.* 9th ed. Boston, MA: Little, Brown & Co.; 1994. pp. 253-256.
111. Kappetein AP, Head SJ, Genereux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodes-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW and Leon MB. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60:1438-54.

16.5 Appendix V: Structured Interview for the Modified Rankin Scale

Modified Rankin Scale	Structured Interview for the Modified Rankin Scale
5=Severe disability: bedridden, incontinent, and requiring constant nursing care and attention	5=Severe disability; someone needs to be available at all times; care may be provided by either a trained or untrained caregiver. Question: Does the person require constant care?
4=Moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance	4=Moderately severe disability; need for assistance with some basic activities of daily living (ADL), but not requiring constant care. Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?
3=Moderate disability: requiring some help, but able to walk without assistance	3=Moderate disability; need for assistance with some instrumental ADL but not basic ADL. Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?
2=Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance	2=Slight disability; limitations in participation in usual social roles, but independent for ADL. Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?
1=No significant disability despite symptoms: able to carry out all usual duties and activities	1=No significant disability; symptoms present but not other limitations. Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?
0=No symptoms at all	0=No symptoms at all; no limitations and no symptoms

Sources:
Modified Rankin Scale: van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Inter-observer agreement for the assessment of handicap in stroke patients. *Stroke*. 1988;19:604-607.
Structured Interview: Wilson JRL, Hareendran A, Grant M, Baird T, Schulz UGR, Muir KW, Bone I. Improving the assessment of outcomes in stroke: Use of a structured interview to assign grades on the Modified Rankin Scale. *Stroke.* 2002;33:2243-2246.

16.6 Appendix VI: NIH Stroke Scale

Note: Additional copies of the NIH Stroke Scale are available on the Internet at the following web sites:

- http://www.ninds.nih.gov/disorders/stroke/strokescales.htm
- http://stroke.nih.gov/resources/scale.htm

You may also call the US National Institute of Neurological Disorders and Stroke (NINDS) Brain Resources and Information Network at (800) 352-9424 to order hard copies. The NIH Stroke Scale is in the Public domain and may be copied and distributed without restriction.

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

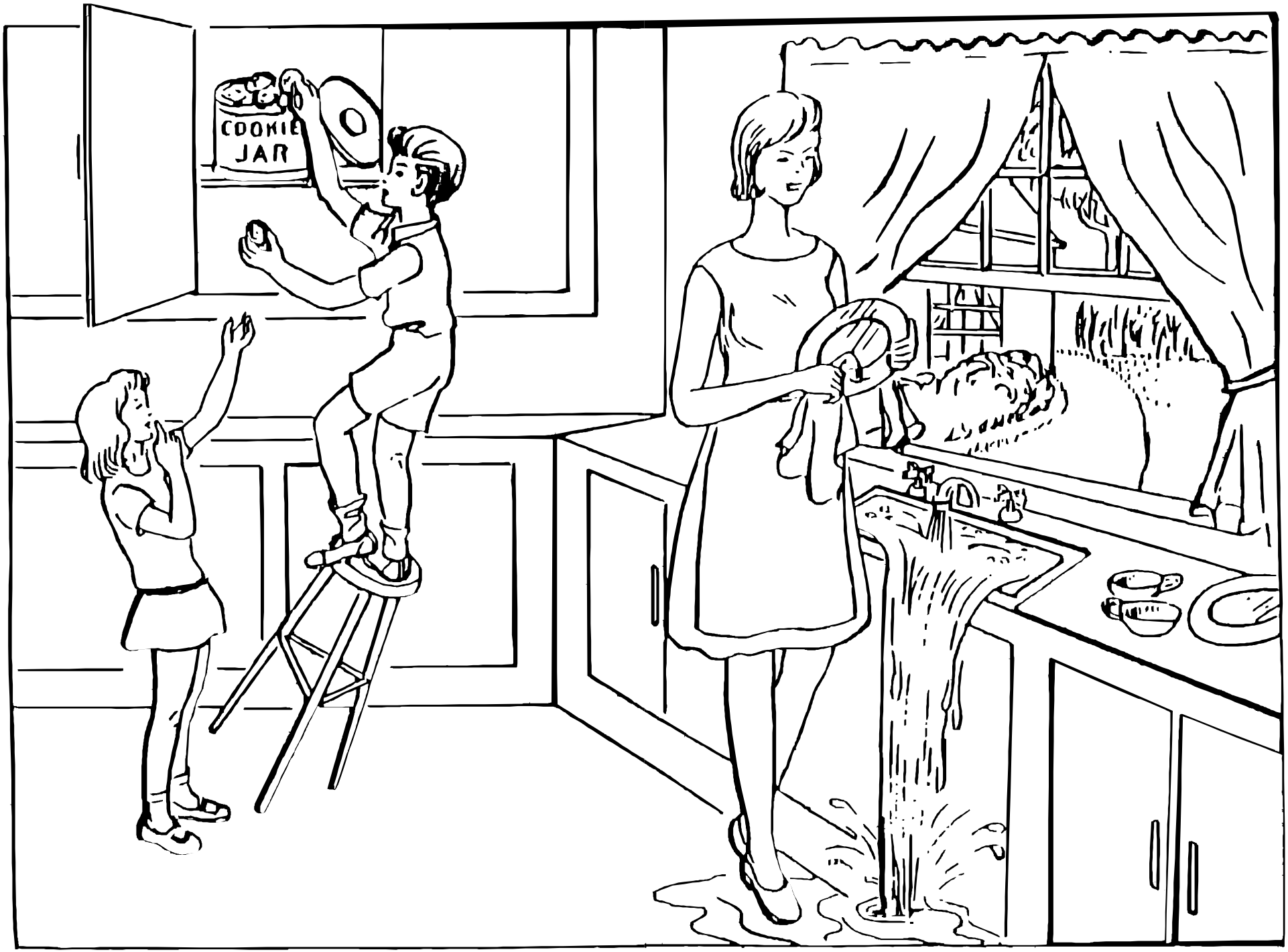
Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

_____

_____


COOKIE
JAR

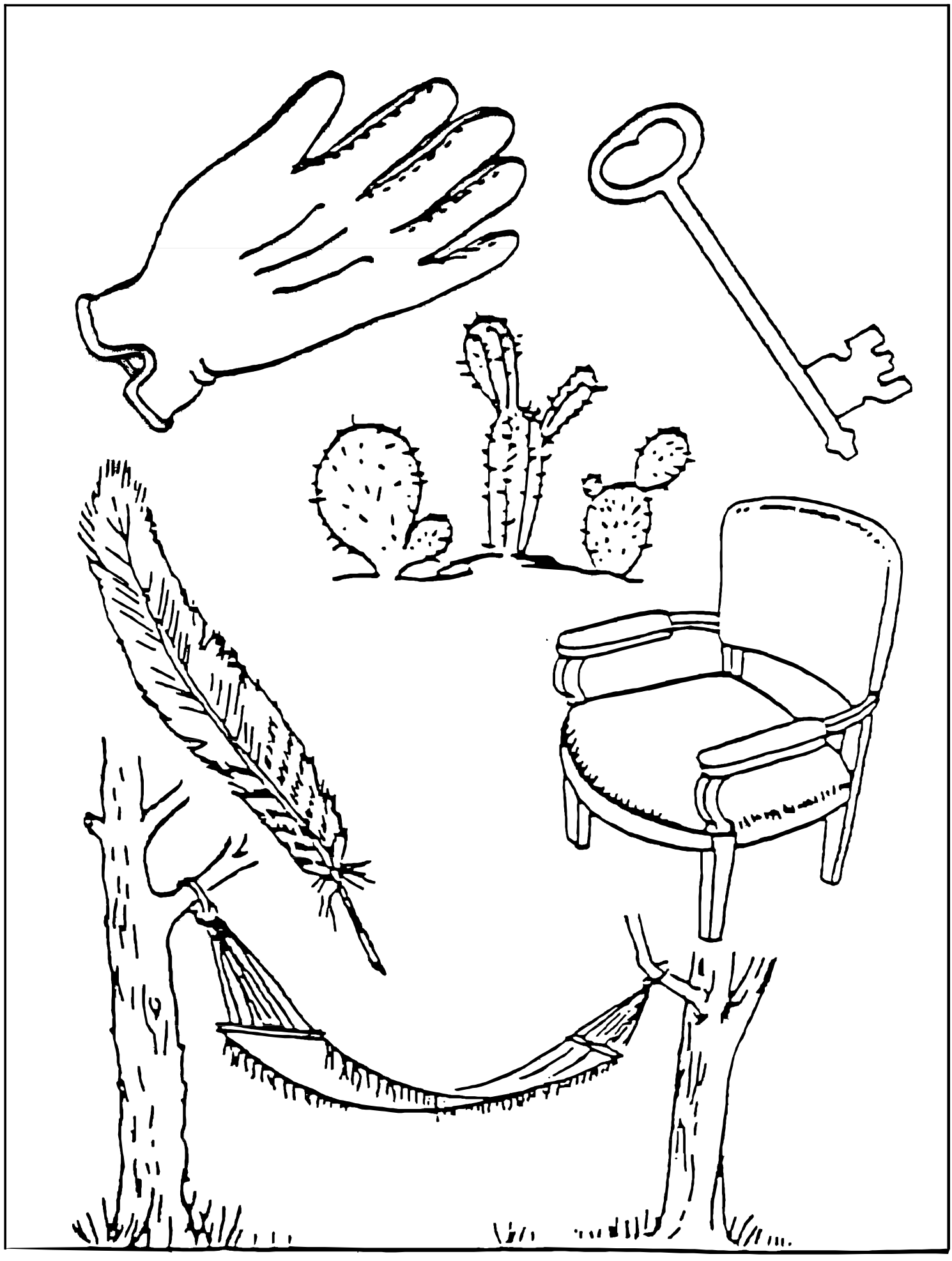
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

16.7 Appendix VII: Neuropsychological Test Battery

Note: Instructions and score sheet forms for the components of the Neuropsychological Test Battery are provided below. Please refer to the Neuropsychological Battery Manual of Operations for additional information.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is administered as a component of the Neuropsychological Test Battery. The RBANS test is copyright NCS Pearson, Inc., and is licensed for use in this trial; authorized copies, alternate versions, and translations will be provided as required. It is provided below for informational purposes.

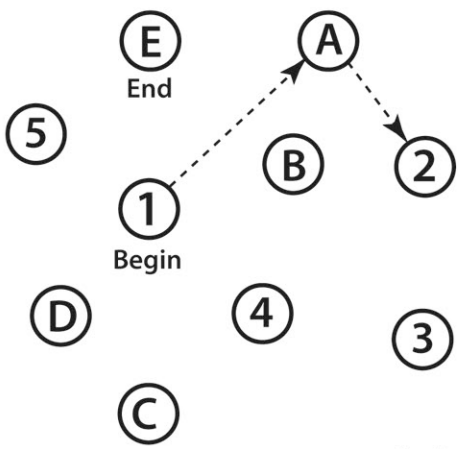
The Trail Making Tests Parts A and B are administered as a component of the Neuropsychological Test Battery. The test forms are in the public domain and are provided below for informational purposes. Administration instructions are licensed for use in this trial and will be provided as required, along with additional test forms.

MONTREAL COGNITIVE ASSESSMENT (MOCA)

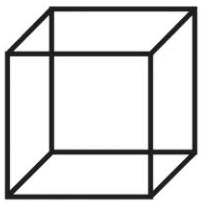
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



[ ]



Copy cube

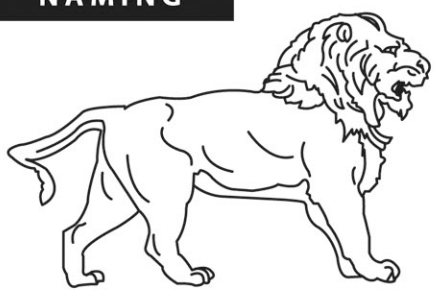
[ ]

Draw CLOCK (Ten past eleven)
(3 points)

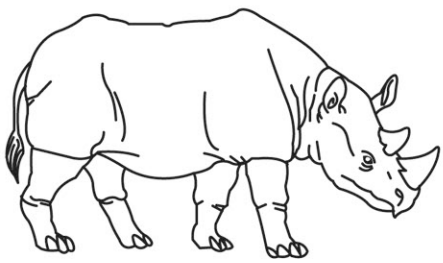
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

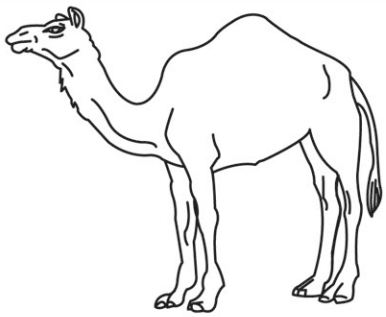
NAMING



[ ]



[ ]



[ ]

___/3

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

___/1

ABSTRACTION

Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

___/2

DELAYED RECALL

Optional

	FACE	VELVET	CHURCH	DAISY	RED
Has to recall words **WITH NO CUE**	[ ]	[ ]	[ ]	[ ]	[ ]
Category cue					
Multiple choice cue					

Points for UNCUED recall only

___/5

ORIENTATION

[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

___/6

www.mocatest.org

Normal ≥ 26 / 30

TOTAL ___/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

RBANS UPDATE

Repeatable Battery for the Assessment of Neuropsychological Status

Christopher Randolph

Record Form a

Name _____ Age_____ Sex_____ Education Level _____

Examiner_____ Date of Testing _____ Ethnicity _____

	Immediate Memory	Visuospatial/ Constructional	Language	Attention	Delayed Memory	TOTAL SCALE
Index Score						
Confidence Interval ____%						
Percentile						

Index Score	Percentile Rank	Total Scale Index Score
160	>99.9	160
155	>99.9	155
150	>99.9	150
145	99.9	145
140	99.6	140
135	99	135
130	98	130
125	95	125
120	91	120
115	84	115
110	75	110
105	63	105
100	50	100
95	37	95
90	25	90
85	16	85
80	9	80
75	5	75
70	2	70
65	1	65
60	0.4	60
55	0.1	55
50	<0.1	50
45	<0.1	45
40	<0.1	40

Observations: _____

_____

_____

PEARSON

PsychCorp

7 8 9 10 11 12 A B C D E

Product Number 0158007212

1 List Learning

Trial 1

Say ***I am going to read you a list of words. I want you to listen carefully and, when I finish, repeat back as many words as you can. You don't have to say them in the same order that I do—just repeat back as many words as you can remember, in any order. Okay?***

Trials 2–4

Say ***I am going to read the list again. When I finish, repeat back as many words as you can, even if you have already said them before. Okay?***

Record responses in order.

Scoring: 1 point for each word correctly recalled on each trial.

List	Trial 1	Trial 2	Trial 3	Trial 4
Market				
Package				
Elbow				
Apple				
Story				
Carpet				
Bubble				
Highway				
Saddle				
Powder				

Number Correct					
	+	+	+	=	
	Total Trial 1	Total Trial 2	Total Trial 3	Total Trial 4	Total Score Range=0–40

PEARSON

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Pearson Executive Office 5601 Green Valley Drive Bloomington, MN 55437
800.627.7271 www.PsychCorp.com

2 Story Memory

Trial 1

Say ***I am going to read you a short story. I'd like you to listen carefully and, when I finish, repeat back as much of the story as you can remember. Try and use the same wording, if you can. Okay?***

Read the story below, then say ***Now repeat back as much of that story as you can.***

Trial 2

Say ***I am going to read that same story again. When I finish, I want you to again repeat back as much of the story as you can remember. Try to repeat it as exactly as you can.***

Read the story below, then say ***Now repeat back as much of that story as you can.***

Scoring: 1 point for *verbatim* recall of bold, italic words or alternatives, shown below in color within parentheses. Record intrusions or variations in the Responses column.

Story	Trial 1 Responses	Trial 1 Score (0 or 1)	Trial 2 Responses	Trial 2 Score (0 or 1)	Item Score (0–2)
1. On ***Tuesday,***					
2. ***May***					
3. ***Fourth,***					
4. in ***Cleveland,*** Ohio,					
5. a ***3 alarm***					
6. ***fire*** broke out.					
7. ***Two***					
8. ***hotels***					
9. and a ***restaurant***					
10. were ***destroyed***					
11. before the ***firefighters (firemen)***					
12. were able to ***extinguish it (put it out).***					
				Total Score (Trial 1 + Trial 2) Range=0–24	

3 Figure Copy

Time Limit: 4 minutes

Fold this page back and present the Figure Copy Drawing Page along with the stimulus. Ask the examinee to make an exact copy of the figure. Tell the examinee that he or she is being timed, but that the score is based *only* on the exactness of his or her copy.

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet A for complete scoring criteria and scoring examples.

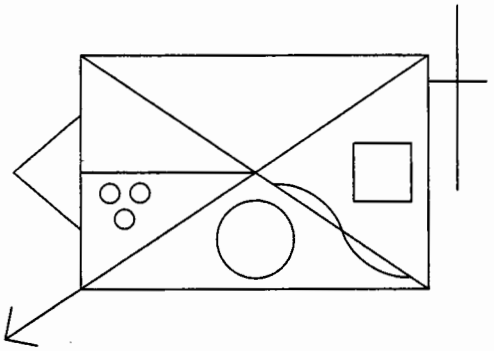


Figure Copy Criteria

(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Criteria
1. rectangle				**Drawing:** lines are unbroken and straight; angles 90 degrees; top/bottom lines 25% longer than sides **Placement:** not rotated more than 15 degrees
2. diagonal cross				**Drawing:** lines are unbroken and straight and should approximately bisect each other **Placement:** ends of lines should meet corners of the rectangle without significant overlap or measurable distance between the ends of the lines and the corners
3. horizontal line				**Drawing:** line is unbroken and straight; should not exceed 1/2 the length of the rectangle **Placement:** should bisect left side of the rectangle at approximately a right angle and intersect the diagonal cross
4. circle				**Drawing:** round, unbroken and closed; diameter should be approximately 1/4–1/3 height of rectangle **Placement:** placed in appropriate segment; not touching any other part of figure
5. 3 small circles				**Drawing:** round, unbroken and closed; equal size; triangular arrangement; not touching each other **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than 15 degrees
6. square				**Drawing:** must be closed; 90 degree angles; lines straight and unbroken; height is 1/4–1/3 height of rectangle **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than 15 degrees
7. curving line				**Drawing:** 2 curved segments are approximately equal in length and symmetrical; correct direction of curves **Placement:** ends of line touch diagonal; do not touch corner of rectangle or intersection of diagonal lines
8. outside cross				**Drawing:** vertical line of the outside cross is parallel to side of rectangle; >1/2 the height of rectangle; horizontal line crosses vertical at 90 degree angle and is between 20–50% of length of vertical line **Placement:** horizontal line of outside cross touches rectangle higher than 2/3 the height of rectangle, but below top; does not penetrate the rectangle
9. triangle				**Drawing:** angle formed by 2 sides of triangle is between 60–100 degrees; sides are straight, unbroken and meet in a point; distance on vertical side of rectangle subsumed by triangle is approximately 50% of the height of vertical side **Placement:** roughly centered on the left vertical side of the rectangle
10. arrow				**Drawing:** straight and unbroken; lines forming arrow are approximately equal in length and not more than 1/3 length of staff **Placement:** must protrude from appropriate corner of rectangle such that staff appears to be continuation of diagonal cross
		Total Score Range=0–20		

Figure Copy Drawing Page

(Fold back for use.)

4 Line Orientation

Time Limit: 20 seconds/item

Present the sample item, and say ***These two lines down here*** (indicate) ***match two of the lines on top. Can you tell me the numbers, or point to the lines that they match?*** Correct any errors and make sure the examinee understands the task. Continue with Items 1–10.

Scoring: 1 point for each line correctly identified.

Item	Responses	Correct Responses	Score (0, 1, or 2)
Sample		1, 7	
1.		10, 12	
2.		4, 11	
3.		6, 9	
4.		8, 13	
5.		2, 4	

Item	Responses	Correct Responses	Score (0, 1, or 2)
6.		1, 6	
7.		3, 10	
8.		5, 8	
9.		1, 3	
10.		11, 13	
		Total Score Range=0–20	

5 Picture Naming

Time Limit: 20 seconds/item

Ask the examinee to name each picture. Give the semantic cue only if the picture is obviously misperceived.

Scoring: 1 point for each item that is correctly named spontaneously or following semantic cue.

Item	Semantic Cue	Responses	Score (0 or 1)
1. chair	a piece of furniture		
2. pencil	used for writing		
3. well	you get water from it		
4. giraffe	an animal		
5. sailboat	used on the water (if "boat," query "what kind")		
6. cannon	a weapon, used in war		
7. pliers	a tool		
8. trumpet	a musical instrument ("cornet" okay)		
9. clothespin	used to hold laundry on a line		
10. kite	it's flown in the air		
		Total Score Range=0–10	

6 Semantic Fluency

Time Limit: 60 seconds

Say ***Now I'd like you to tell me the names of all of the different kinds of fruits and vegetables that you can think of. I'll give you one minute to come up with as many as you can. Ready?***

Scoring: 1 point for each correct response.

1. _____	11. _____	21. _____	31. _____
2. _____	12. _____	22. _____	32. _____
3. _____	13. _____	23. _____	33. _____
4. _____	14. _____	24. _____	34. _____
5. _____	15. _____	25. _____	35. _____
6. _____	16. _____	26. _____	36. _____
7. _____	17. _____	27. _____	37. _____
8. _____	18. _____	28. _____	38. _____
9. _____	19. _____	29. _____	39. _____
10. _____	20. _____	30. _____	40. _____

Total Score
Range=0–40 ☐

7 Digit Span

Say ***I am going to say some numbers, and I want you to repeat them after me. Okay?***
Read the numbers at the rate of 1 per second. Only read the second string in each set if the first string was failed. Discontinue after failure of both strings in any set.

Scoring: 2 points for the first string correct, 1 point for the second string correct, and 0 points for both strings failed.

Item	First String	String Score (0 or 2)	Second String	String Score (0 or 1)	Item Score (0–2)
1.	**4—9**		**5—3**		
2.	**8—3—5**		**2—4—1**		
3.	**7—2—4—6**		**1—6—3—8**		
4.	**5—3—9—2—4**		**3—8—4—9—1**		
5.	**6—4—2—9—3—5**		**9—1—5—3—7—6**		
6.	**2—8—5—1—9—3—7**		**5—3—1—7—4—9—2**		
7.	**8—3—7—9—5—2—4—1**		**9—5—1—4—2—7—3—8**		
8.	**1—5—9—2—3—8—7—4—6**		**5—1—9—7—6—2—3—6—5**		

Total Score
Range=0–16 ☐

8 Coding

Time Limit: 90 seconds

Say ***Look at these boxes*** (indicate key)***. For each one of these marks there is a number that goes with it. Down here there are marks, but no numbers. I want you to fill in the number that goes with each mark.***

Demonstrate the first three. Say ***Now I would like you to fill in the rest of these boxes up to the double lines*** (indicate) ***for practice.*** Correct any errors as they are made. Make sure that the examinee understands the task and has correctly completed the sample items before you begin timing.

Say ***Now I would like you to continue to fill in the numbers that match the marks. Go as quickly as you can without skipping any. When you reach the end of the line, go on to the next one. Ready? Go ahead.***

Redirect the examinee to the task if he or she becomes distracted. If the examinee is unable to comprehend the task, the subtest score is 0.

Scoring: 1 point for each item correctly coded within 90 seconds (*do not* score the sample items).

Note: Familiarize yourself with these instructions before administering this subtest.

Total Score Range=0–89	

9 List Recall

Say ***Do you remember the list of words that I read to you in the beginning? Tell me as many of those words as you can remember now.***

Scoring: 1 point for each word correctly recalled.

List (Do not read.)	Response	Score (0 or 1)
Market		
Package		
Elbow		
Apple		
Story		
Carpet		
Bubble		
Highway		
Saddle		
Powder		
	Total Score Range=0–10	

10 List Recognition

Say ***I'm going to read you some words. Some of these words were on that list, and some of them weren't. I want you to tell me which words were on the list.*** For each word, ask ***Was_____ on the list?***

Scoring: 1 point for each word correctly identified. Circle the letter corresponding to examinee's response (y = yes, n = no); bold, capitalized (**Y, N**) letter indicates correct response.

List	Circle One		List	Circle One		List	Circle One		List	Circle One	
1. **Apple**	**Y**	n	6. sailor	y	**N**	11. **Bubble**	**Y**	n	16. **Saddle**	**Y**	n
2. honey	y	**N**	7. velvet	y	**N**	12. prairie	y	**N**	17. **Powder**	**Y**	n
3. **Market**	**Y**	n	8. **Carpet**	**Y**	n	13. **Highway**	**Y**	n	18. angel	y	**N**
4. **Story**	**Y**	n	9. valley	y	**N**	14. oyster	y	**N**	19. **Package**	**Y**	n
5. fabric	y	**N**	10. **Elbow**	**Y**	n	15. student	y	**N**	20. meadow	y	**N**
									Total Score Range=0–20		

11 Story Recall

Say ***Do you remember that story about a fire that I read to you earlier? Tell me as many details from the story as you can remember now.***

Scoring: 1 point for each *verbatim* recall of bold, italic words or alternatives, shown below in color within parentheses. Record intrusions or variations in the Responses column.

Story (Do not read.)	Responses	Item Score (0 or 1)
1. On ***Tuesday,***		
2. ***May***		
3. ***Fourth,***		
4. in ***Cleveland,*** Ohio,		
5. a ***3 alarm***		
6. ***fire*** broke out.		
7. ***Two***		
8. ***hotels***		
9. and a ***restaurant***		
10. were ***destroyed***		
11. before the ***firefighters*** *(firemen)*		
12. were able to ***extinguish it*** *(put it out).*		
	Total Score Range=0–12	

12 Figure Recall

Say ***Do you remember that figure that I had you copy? I want you to draw as much of it as you can remember now. If you remember a part, but you're not sure where it goes, put it anywhere. Try to draw as much of it as you can.***

Now, present the Figure Recall Drawing Page.

Scoring: 1 point for correctness and completeness (drawing), and 1 point for proper placement. See Appendix 1 in Stimulus Booklet A for complete scoring criteria and scoring examples.

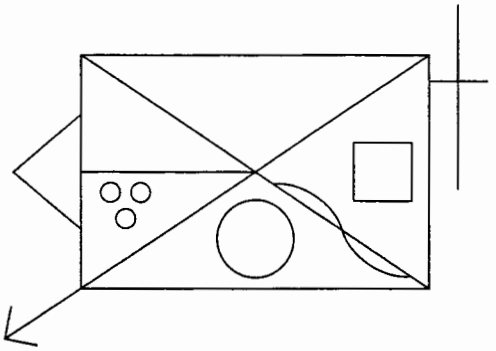


Figure Recall Criteria

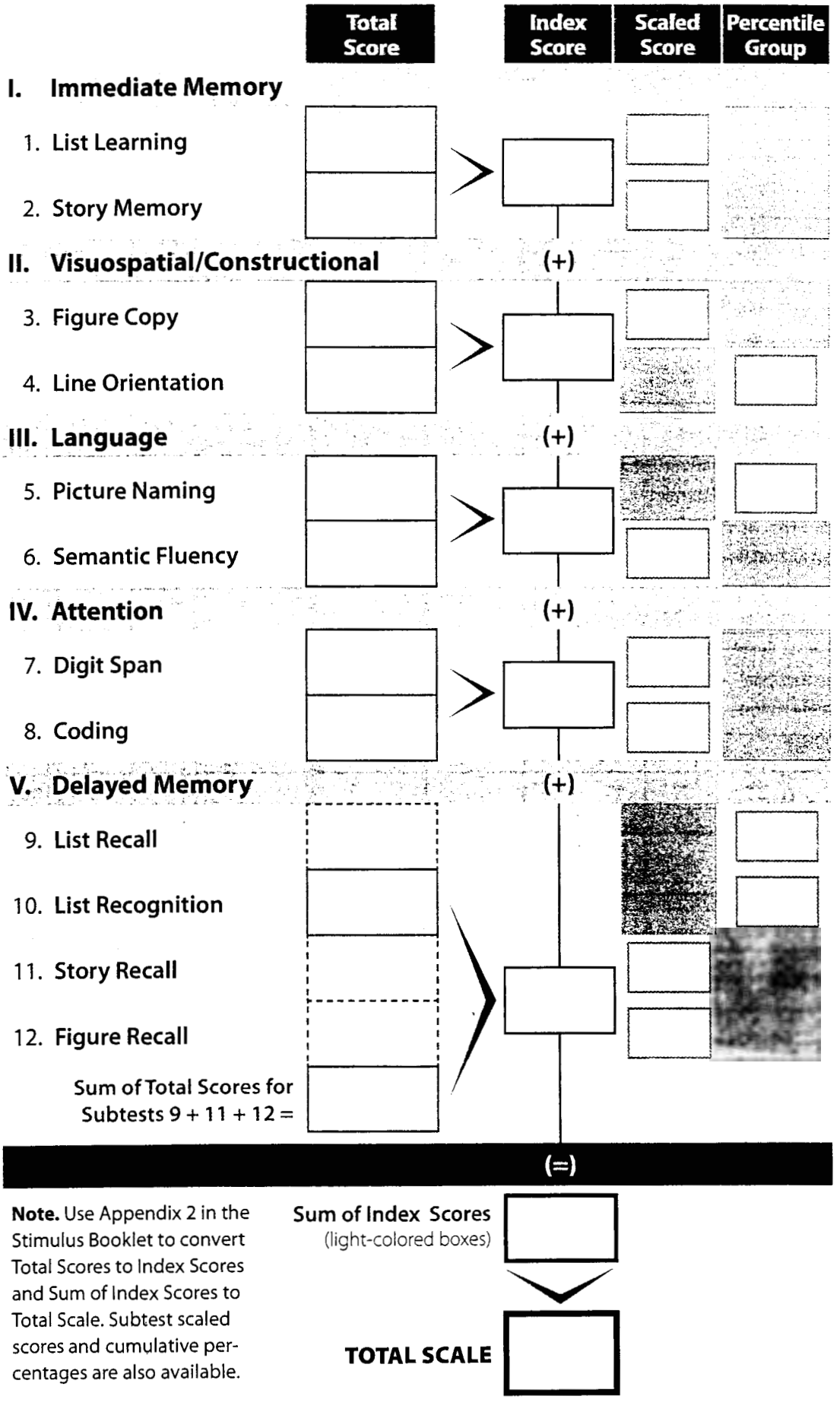
(Fold back for use.)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0, 1, or 2)	Scoring Criteria
1. rectangle				**Drawing:** lines are unbroken and straight; angles 90 degrees; top/bottom lines 25% longer than sides **Placement:** not rotated more than 15 degrees
2. diagonal cross				**Drawing:** lines are unbroken and straight and should approximately bisect each other **Placement:** ends of lines should meet corners of the rectangle without significant overlap or measurable distance between the ends of the lines and the corners
3. horizontal line				**Drawing:** line is unbroken and straight; should not exceed 1/2 the length of the rectangle **Placement:** should bisect left side of the rectangle at approximately a right angle and intersect the diagonal cross
4. circle				**Drawing:** round, unbroken and closed; diameter should be approximately 1/4–1/3 height of rectangle **Placement:** placed in appropriate segment; not touching any other part of figure
5. 3 small circles				**Drawing:** round, unbroken and closed; equal size; triangular arrangement; not touching each other **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than 15 degrees
6. square				**Drawing:** must be closed; 90 degree angles; lines straight and unbroken; height is 1/4–1/3 height of rectangle **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than 15 degrees
7. curving line				**Drawing:** 2 curved segments are approximately equal in length and symmetrical; correct direction of curves **Placement:** ends of line touch diagonal; do not touch corner of rectangle or intersection of diagonal lines
8. outside cross				**Drawing:** vertical line of the outside cross is parallel to side of rectangle; >1/2 the height of rectangle; horizontal line crosses vertical at 90 degree angle and is between 20–50% of length of vertical line **Placement:** horizontal line of outside cross touches rectangle higher than 2/3 the height of rectangle, but below top; does not penetrate the rectangle
9. triangle				**Drawing:** angle formed by 2 sides of triangle is between 60–100 degrees; sides are straight, unbroken and meet in a point; distance on vertical side of rectangle subsumed by triangle is approximately 50% of the height of vertical side **Placement:** roughly centered on the left vertical side of the rectangle
10. arrow				**Drawing:** straight and unbroken; lines forming arrow are approximately equal in length and not more than 1/3 length of staff **Placement:** must protrude from appropriate corner of rectangle such that staff appears to be continuation of diagonal cross
		Total Score Range=0–20		

Figure Recall Drawing Page

(Fold back for use.)

Score Conversion Page



Note. Use Appendix 2 in the Stimulus Booklet to convert Total Scores to Index Scores and Sum of Index Scores to Total Scale. Subtest scaled scores and cumulative percentages are also available.

Supplemental Discrepancy Analysis Page

Index Differences

Score 1–Score 2	Score 1	Score 2	Difference	Statistical Significance _____Level	Frequency of Difference in Standardization Sample
Immediate Memory—Visuospatial/Constructional					
Immediate Memory—Attention					
Immediate Memory—Language					
Immediate Memory—Delayed Memory					
Immediate Memory—Total Scale					
Visuospatial/Constructional—Attention					
Visuospatial/Constructional—Language					
Visuospatial/Constructional—Delayed Memory					
Visuospatial/Constructional—Total Scale					
Attention—Language					
Attention—Delayed Memory					
Attention—Total Scale					
Language—Delayed Memory					
Language—Total Scale					
Delayed Memory—Total Scale					

⊂	∧	=	┘	∨	⊃	+	⊥	⊢
1	2	3	4	5	6	7	8	9

SAMPLE________________________________

=	⊢	⊂	∧	+	┘	⊥	⊃	∨	=	⊢	∧	⊃	+

⊥	⊃	∨	⊢	=	∧	⊂	+	┘	∧	⊥	⊂	+	┘

⊃	⊢	∧	=	∨	⊂	┘	+	⊥	=	⊃	∧	⊢	⊂

+	⊂	⊢	┘	=	⊢	+	∧	⊃	⊂	┘	⊥	+	⊢

⊂	+	⊢	⊃	∧	=	⊥	┘	⊂	=	+	∨	⊥	∧

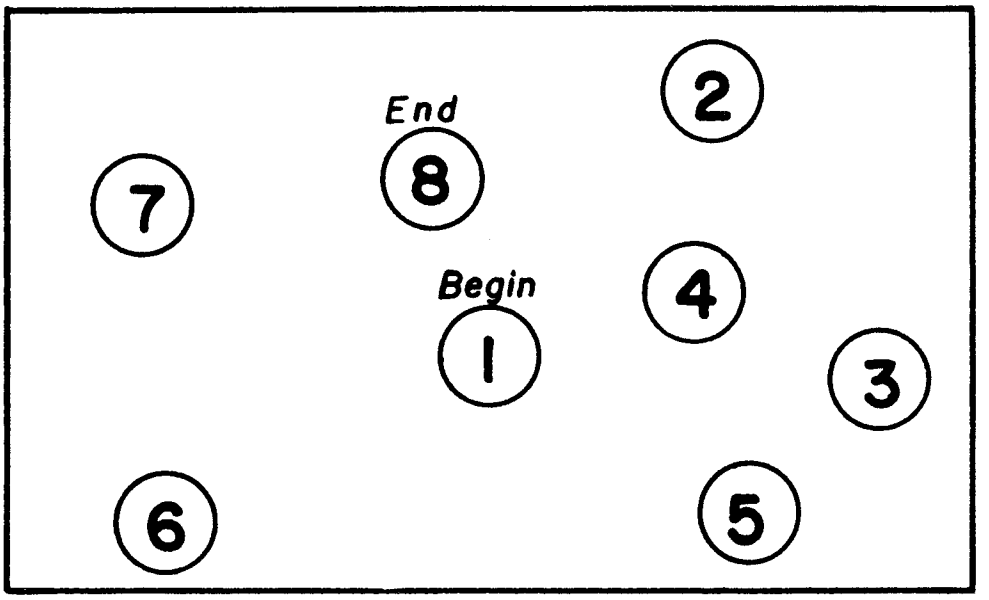
∧	=	┘	⊢	+	∨	⊥	┘	∧	⊃	∨	⊥	⊂	┘

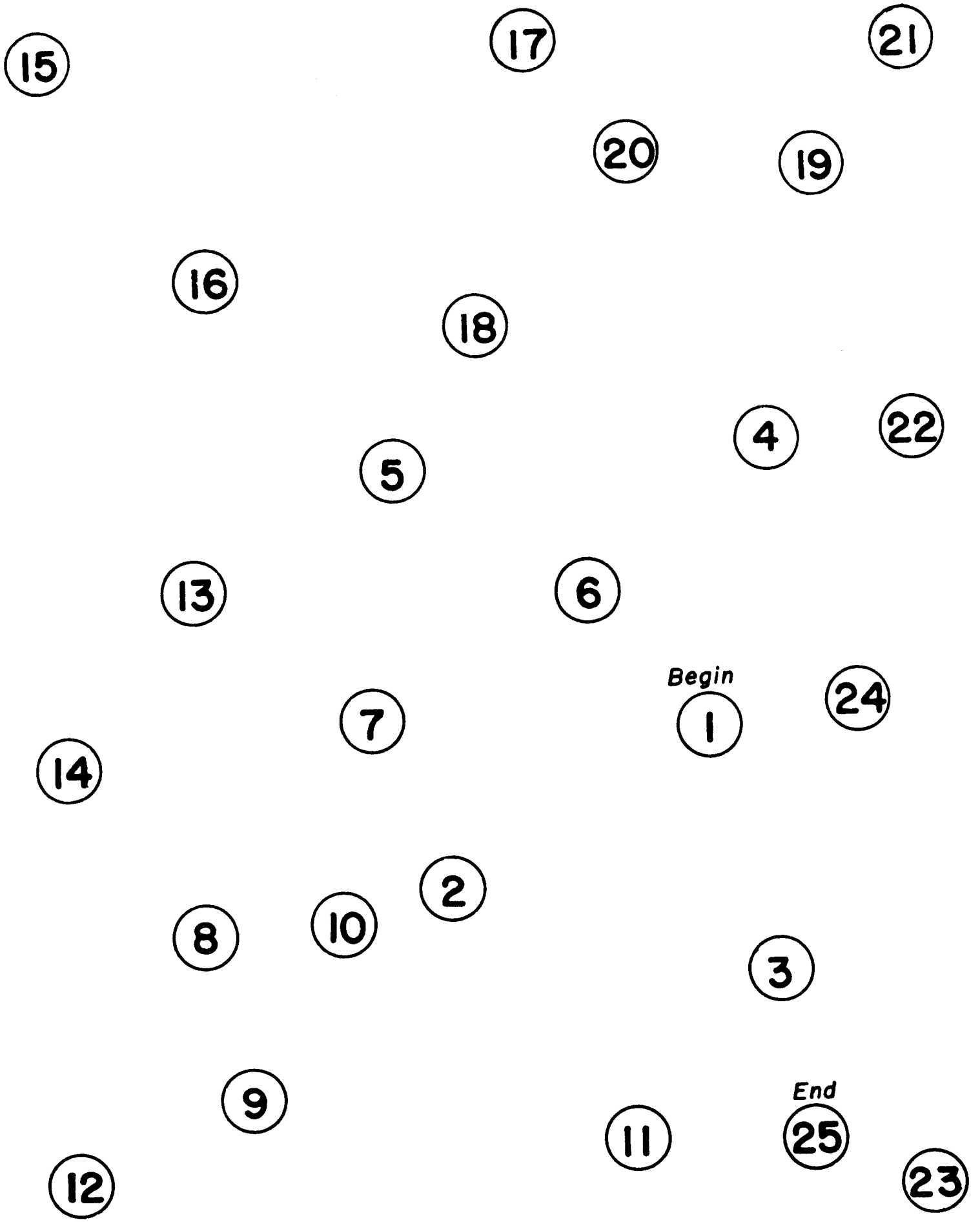
+	⊂	┘	⊃	∧	=	⊂	+	⊥	∨	┘	∧	⊃	=

TRAIL MAKING

Part A

SAMPLE

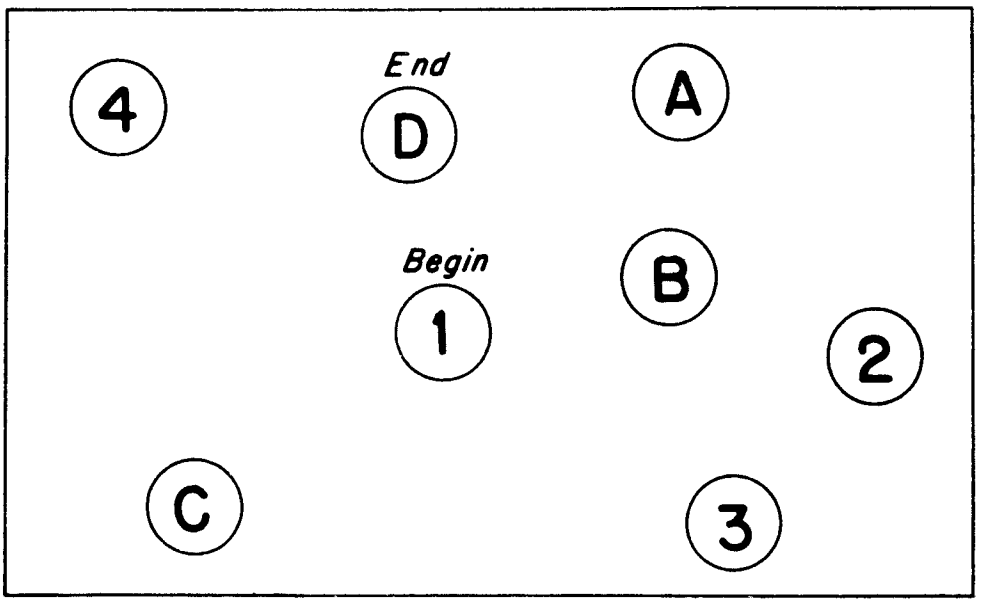


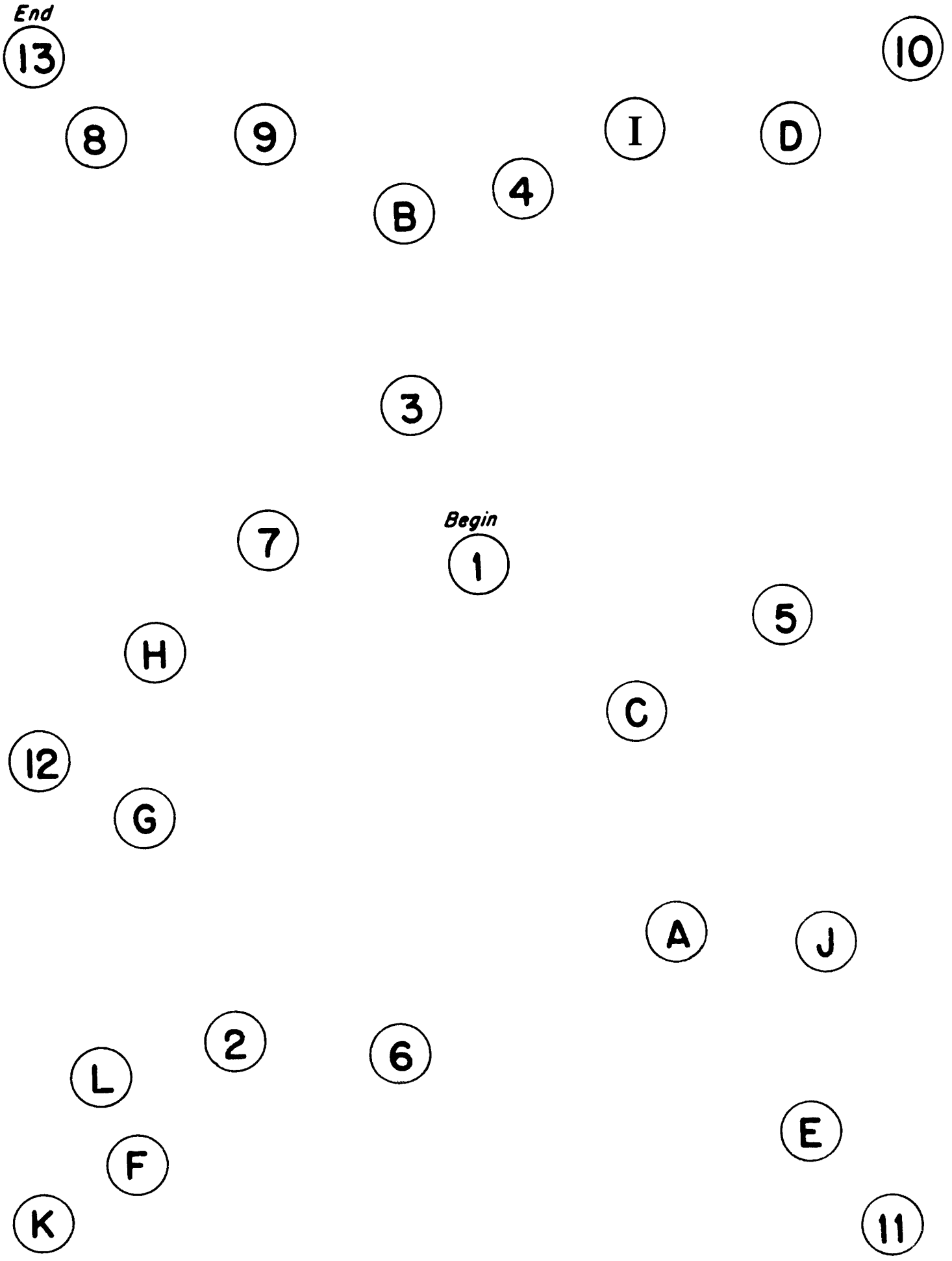

15
17
21
20
19
16
18
4
22
5
13
6
Begin
24
7
1
14
2
8
10
3
9
End
11
25
12
23

TRAIL MAKING

Part B

SAMPLE




End
13
10
8
9
I
D
4
B
3
7
Begin
1
5
H
C
12
G
A
J
2
6
L
E
F
K
11

16.8 Appendix VIII: Angiographic Imaging Acquisition Guidelines

REFLECT TRIAL

Angiographic Acquisition Guidelines

All angiograms should be obtained paying strict attention to the following features:

1. Acquire all standard procedural fluoroscopic/angiograms in DICOM format at the highest magnification which will still incorporate the entire segment of the aortic arch and the ostia of the 3 major cerebral vessel takeoffs (innominate, left carotid and left subclavian).
2. All images should have subject identifiers removed prior to uploading images to the web-based image transfer system. Imaging studies should be appropriately labeled with Study Name, site ID, subject ID and date that the imaging study was performed.
3. Submit the best LAO projection for assessment of the Aortic Arch and the 3 major cerebral vessel takeoffs (innominate, left carotid and left subclavian). If renal dysfunction or other clinical concerns limit contrast administration, angiography of the innominate artery alone is sufficient. All subsequent fluoroscopic/angiographic images should be taken using the same LAO projection that was used for the initial assessment.
4. Submit fluoroscopic images using the initial arch projection to document proper device positioning at the following recommended time points:
    - After deployment of the TriGuard™ HDH or TriGUARD *3*, angiography of the device and the entire arch is strongly recommended and can be done during or after pigtail placement.
    - Tracking of the TAVR delivery system to the aortic annulus
    - Final deployment of the first prosthetic valve
    - Removal of the TAVR delivery system (after any additional post-dilatation or additional valve implantations have been completed)
    - If the position of the TriGuard™ HDH or TriGUARD *3* is perceived to have changed during the procedure, repeat arch assessment with contrast is strongly recommended.
5. Provide a plain, non-contrast image of any device complication or malfunction observed during the procedure.

PLEASE TRY TO INCLUDE IN YOUR SUBMISSION:

1. Cath Lab Procedure Log or Technician's Worksheet Form (Please keep a copy of the original). This may be scanned and emailed to the Angiographic Core Laboratory contact at the email address below:

Phase I: Ecaterina Cristea, MD
Yale Angiographic Core Laboratory
ecaterina.cristea@yale.edu

Phase II: Ivana Jankovic, MD
CRF Core Lab Operations
ijankovic@crf.org

2. Procedural films. Angiographic and fluoroscopic imaging studies will be uploaded by the site to a web-based imaging media transfer system (Intelemage®, LLC, Cincinnati, OH USA).

Phase I: **Yale Angiographic Core Lab Contact:**
Ecaterina Cristea, MD
YALE CARDIOVASCULAR RESEARCH GROUP
REFLECT TRIAL
Yale Angiographic Core Laboratory
Yale University School of Medicine
135 College Street, Suite 101
New Haven, CT 06510
(203) 737-2275 (Office)
(203) 737-7457 (Office Fax)
ecaterina.cristea@yale.edu

Phase II: **Cardiovascular Research Foundation Core Lab Contact:**
Ivana Jankovic, MD
Director, Core Lab Operations
Cardiovascular Research Foundation
Clinical Trials Center
1700 Broadway, 9th Floor
New York, NY 10019
Tel: (646) 434-4388
Fax: (646) 434-4711
ijankovic@crf.org

16.9 Appendix IX: Magnetic Resonance Imaging Acquisition Protocol

The REFLECT Study

Magnetic Resonance Imaging Core Laboratory

Cerebral MRI Acquisition Guidelines

Table of Contents

1.0 Introduction

The REFLECT Study is designed to evaluate the safety and efficacy of the Keystone Heart TriGuard™ HDH and TriGUARD *3* in reducing neuro-embolic consequences of Transcatheter Aortic Valve Replacement (TAVR). The study is designed as a prospective, randomized, multi-center study.

During the course of the study, efficacy of the TriGuard device will be evaluated through the analysis of cerebral lesions identified in the DWMRI data.

Diffusion weighted imaging (DWI) is a sequence particularly sensitive to the presence of recent ischemic damage that may arise as a result of emboli and T2* weighted gradient echo (T2* GRE) is a sequences particularly sensitive to the presence of certain blood products.

1.1 Equipment Requirements

- 1.5 Tesla MRI Scanner
- Dedicated head coil (preferably multichannel receive-only coil)

1.2 Scans to be acquired

DWMRI brain scans will be acquired according to the endpoints and REFLECT study protocol.

Each scan is comprised of localizer sequences for planning purposes followed by 4 diagnostic sequences in the axial plane. The total estimated acquisition time is 13 minutes.

2.0 Image Acquisition Guidelines

2.1 Step 1: Patient preparation

- **Pre-scan safety checks to exclude contraindications to MRI scanning must be undertaken in compliance with established local protocols**
- All jewelry and metallic objects removed from patient's waist upwards (including bra straps containing metal fasteners).
- Acoustic protection provided (e.g. ear plugs or headphones).
- Head coil positioned and foam padding used where necessary to ensure the head is adequately immobilized.
- Padding placed under patient's knees for comfort.
- laser light positioned at the nasion.
- Patient requested to avoid the use of hair spray, hair gel, or other hair treatment products.
- Patients requested to avoid the use of face and eye makeup products.

2.2 Step 2: Localiser sequences and planning

The localizer sequences used and brain field-of-view (FOV) positioning technique used may be adapted from established local protocols and auto-alignment functions may be used where available. However, in positioning the diagnostic axial scans it is essential that:

1. Identical slice positioning is used for all 4 diagnostic sequences.

2. The FOV is aligned in all 3 planes to achieve a true anatomical axial plane.
3. The axial slices align parallel to the anterior commissure-posterior commissure plane (ac-pc plane)
4. The scans cover the whole brain from at least vertex to foramen magnum.

For those units without established procedures for planning axial brain imaging, an example protocol is provided below. Sample parameters are provided in Table 1.

Step A: 3 plane localizer

Step B: Limited FOV sagittal T1 weighted images planned from coronal and axial localizers with the center slice aligned to the sagittal midline structures in both planes (**Figure 1**).

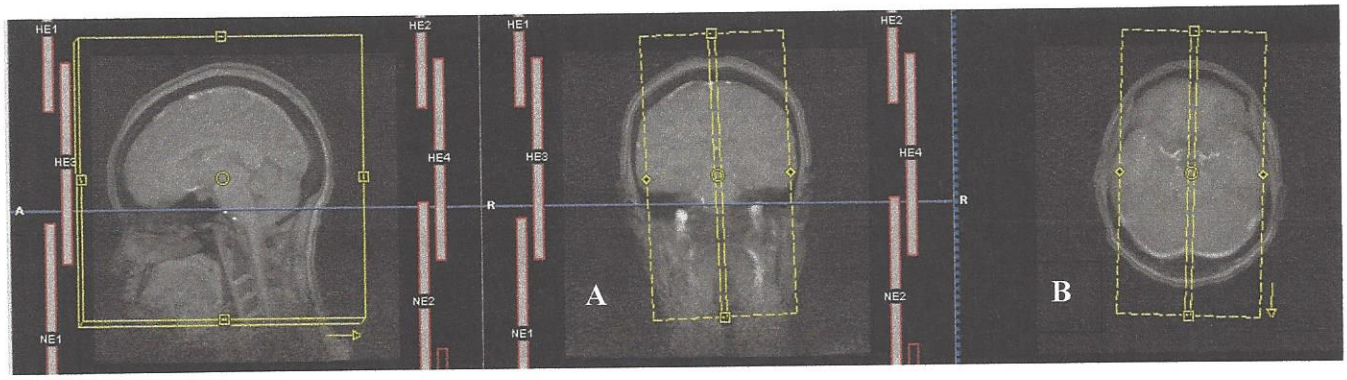


Figure 1. 3 plane localiser used for planning T1 weighted sagittal images. The centre slice is aligned to the sagittal midline structures on the coronal (A) and axial (B) images. Note that the sagittal images are for planning only and do not need to cover the whole brain in the axial and coronal planes.

Step C: Slices for the axial sequences are angled parallel to ac-pc plane (**Figures 2 & 3**) and the FOV covers the whole brain. The center slice should have the same position for all 4 diagnostic scans.

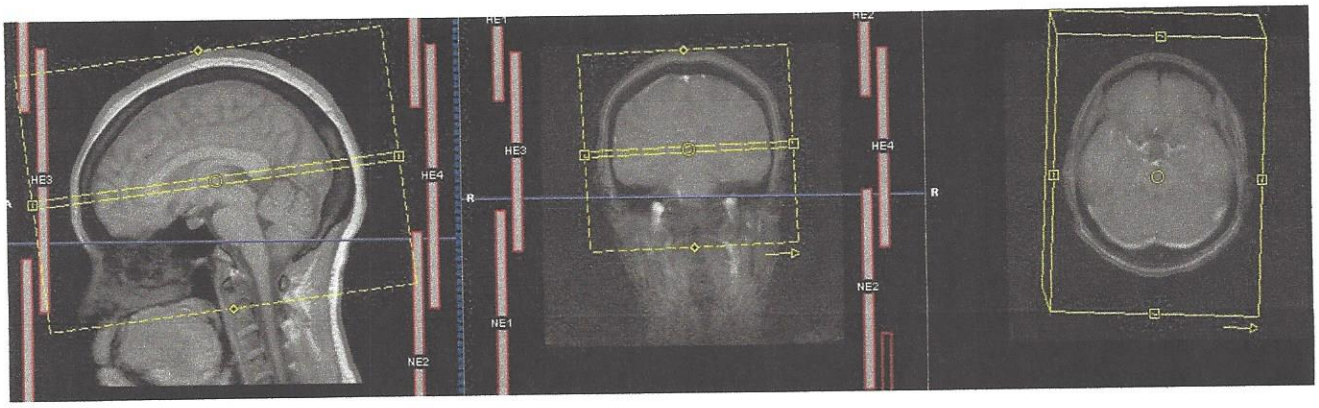


Figure 2. T1 weighted sagittal localizer (left) plus coronal and axial images from previous 3-plane localizer used for planning the 4 axial diagnostic sequences. The ac-pc plane is planned from the mid sagittal images.

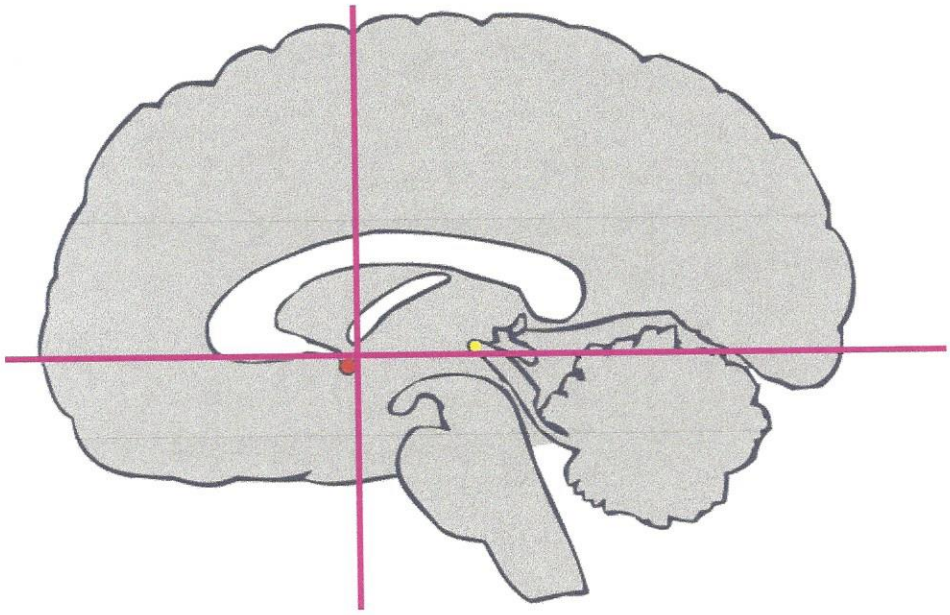


Fig 3. Locating the ac-pc line. The anterior commissure (ac) (red dot), the posterior commissure (pc) (yellow dot). The ac-pc line passes from the superior surface of the ac through the center of the pc (purple horizontal line). ref:http://ccn.ucla.edu/wiki/index.php/Find_the_AC-PC_line

Table 1. Example parameters for the planning sequences

Sequence	**3 plane localiser**			**Sagittal planning sequence**
Orientation	Sagittal	Axial	Coronal	Sagittal
Phase encode direction	A-P	A-P	R-L	A-P
In-plane FOV in mm (RL x AP)	260 x 260			240 x 240
Slices	5			19
Slice thickness (mm)	8			5
Interslice gap (mm)	2			1.5
True in-plane resolution (mm)	1.4 x 1.0			0.9 x 0.9
TR (ms)	7			195
TE (ms)	2.95			4.76
Averages	2			1
Estimated acquisition time	42 sec			29 Ec

2.3 Step 3: Diagnostic Sequences

All 4 sequences are performed in the axial plane, with identical slice positioning and in the order below. Mandatory sequence parameters that must be used are provided in **table 2**.

1. Diffusion weighted imaging (**DWI**)
2. T2-weighted turbo spin echo (**T2w TSE or equivalent**)
3. T2-weighted gradient echo (**T2*w GRE or equivalent**)
4. Fluid attenuated inversion recovery (**FLAIR or equivalent**)

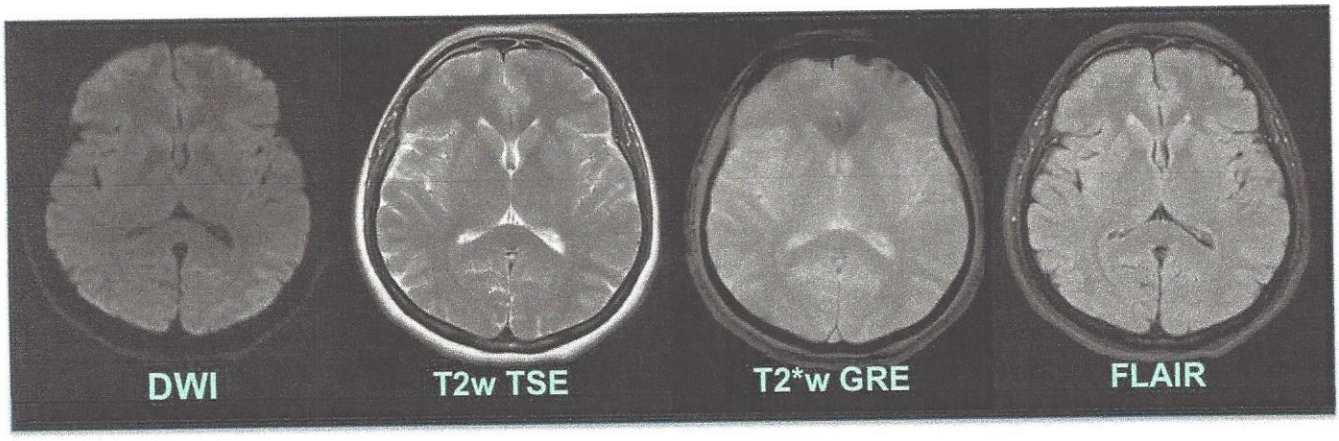


Figure 4. Examples of images from the 4 diagnostic axial sequences

Table 2. Mandatory parameters for 4 diagnostic sequences

Sequence	**DWI**	**T2w TSE** (or equivalent eg FSE)	**T2w GRE** (or equivalent eg FLASH)	**T2w FLAIR** (or equivalent eg TIRM)
Orientation	Axial	Axial	Axial	Axial
Acquisition type	2D (multislice)	2D (multislice)	2D (multislice)	2D (multislice)
Phase encode direction	A-P	R-L	R-L	R-L
In-plane FoV in mm (APxRL)	240 x 240	240 x 180	240 x 240	240 x180
Slices	39 or full head	29	29	29
Slice thickness (mm)	4	5	5	5
Interslice gap (mm)	0	0.75	0.75	0.75
Acquisition matrix (frequency x phase)	192 x 192	512 x 288	256 x 256	256 x 192
True in-plane acquisition resolution (frequency x phase mm)[1]	1.3 x 1.3	0.5 x 0.6	0.9 x 0.9	0.9 x 0.9
TR[2]	4500	5040	997	8000
TE[2]	89	93	26	89
TI[2]				2370
Averages	4	2	1	1
Flip angle (deg)		150	20	150
Turbo factor (TSE)		16		16
DWI b values (mm s^{-2})	0 and 1000			
Diffusion directions	3			
RF pulse type	Normal	Normal	Normal	Normal
Estimated acquisition time	1 min 27	3 min 08	4 min 17	3 min 30

[1]Reconstruction resolution may be higher with interpolation.

[2]Timing parameters may be set to the closest allowed value, if the scanner only allows changes on certain steps.

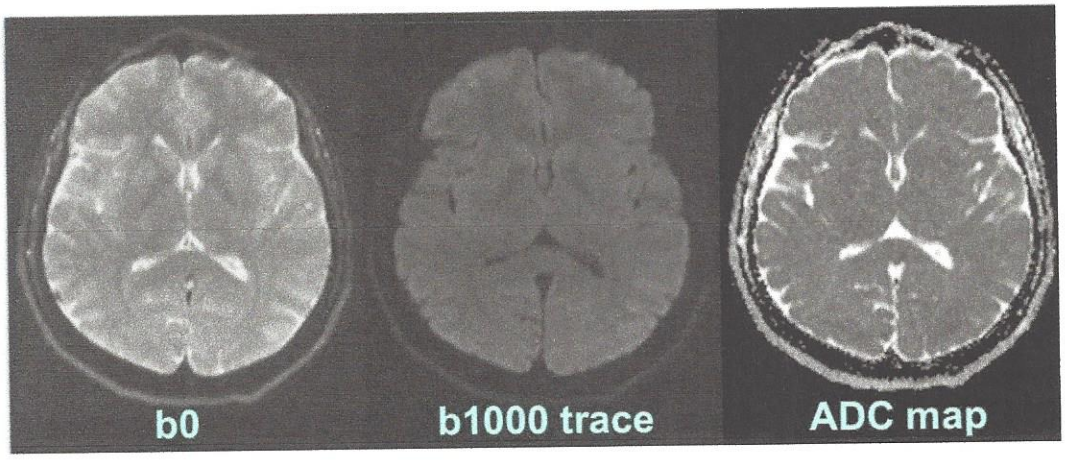
2.4 Step 4: Assess Images for Quality

- All images should be checked for quality before the patient is moved from the scanner. Sequences degraded by artefacts such as excessive movement should be repeated immediately if at all possible.
- The reason for degraded images or incomplete scans to be noted in the data transmission form.

2.5 Step 5: Image Post Processing

- The DWI dataset is processed to provide:
  - **a.** b0 images
  - **b.** b1000 diffusion trace images. This may be combined with the b0 images in a single set of all 26 b0 slices followed by all 26 b1000 trace images. Please do not supply as alternating b0, b1000 images at each slice position.
  - **c.** Apparent diffusion coefficient (**ADC**) map

Please note that many scanners can perform this as an automated task



2.6 Step 6: Prepare Data for Submission

All MRI data will be sent to the data center for independent study analysis.

- Data should be stored in DICOM 3.0 format, not DICOMDAT.
- It is important to note that images from the same "B value" (B 0 or no diffusion weighting, B 1000 or heavy diffusion weighting) DWI images need to be sent so that all of the B 0 images are sent in anatomical order (i.e. B 0 slice 1 followed by B 0 slice 2, B 0 slices 3, etc.) followed by the B 1000 images in anatomical order. B 0 images and B 1000 images should not be innterleaved.
- All available images must have patient identifiers (protected health information (PHI) such as name, date of birth, medical record number) removed at time of image transfer to the data center.
- Please use the following during anonymization:

- **Modality** = MR
- **"Body Part Examined" contains the value** = HEAD
- **"Protocol Name" contains any of the values** = PWI, Brain, Neuro, Perf.
- **"Series Description" contains any of the values** = DWI, T2 FLAIR, T2 GRE, T2 TSE, LOC etc.

- Imaging studies should be labeled as followed: **CCSCTC-SNR**

  CC- is the region ID which will be assigned in two letter format (e.g US, UK).

  SC- is the site ID which will be assigned in two number format (01, 02, etc.).

  TC- is the internal ID which will be assigned in two number format (for REFLECT this number is 09).

  SNR- is the subject number which will be assigned in three number format (001, 002, etc.)

- It should be clearly stated in the data transmission form or the uploading system the protocol time point of the study. However, this information must NOT be incorporated into the DICOM image headers themselves. (i.e. it should not be included in the patient identifier, protocol name, study comment or similar fields).

- Make sure all required images are included:

  1. Localiser images
  2. Axial DWI: to include b0, b1000 trace images and ADC map
  3. Axial T2w TSE
  4. Axial T2*w GRE
  5. Axial T2w FLAIR

Instructions for submission of MRI imaging data will be reviewed with each site during DW-MRI Protocol Training sessions. Images will be sent via electronic transfer using the dedicated transfer solution.

Instructions will be provided during site set-up. You may also reference the transfer solutions Site User Guide and/or the Quick Reference Sheet for specific instructions regarding the electronic transfer of MR images.

3.0 MRI Precautions and Considerations

Standard precautions should be taken into consideration for any patient undergoing MR imaging. Patients should be assessed for history of implantable devices that may have occurred as a result of, or outside of the conduct of the REFLECT Trial. This may include, but is not limited to the following:

- Permanent pacemaker implantation

- Implantable Cardioverter-defibrillator
- Surgical clips or other devices implanted as a result of vascular injury or other complication requiring surgical intervention
- Aortic bioprosthetic valve implanted at the time of trial enrollment for the treatment of senile aortic stenosis

Considerations and precautions for commercially available aortic transcatheter bioprosthetic valves that may be utilized for patients enrolled in the REFLECT Trial:[1]

Edwards SAPIEN 3 Transcatheter Heart Valve[2]

Edwards Life Lifesciences Corporation, Edwards Lifesciences LLC Irvine California, USA

Non-clinical testing has demonstrated that the Edwards SAPIEN THV (implant) is MR compatible. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3 Tesla. Use of 3 Tesla is not allowed per the REFLECT protocol
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 2W/kg for 15 minutes of scanning.
- Normal mode operation, as defined by IEC 60601-2-33 Ed.3.0, of the MR system.

In non-clinical testing and analysis, the implant was determined to produce a temperature rise of less than 1.1°C above background for a whole body SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5T cylindrical whole body MR system, assessed using a GE Signa whole body coil and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.2 W/kg and local background SAR at the site of the implant was 5.6 W/kg. The measured rise above background was 0.7°C for a whole body SAR of 2 W/kg in a 3.0T cylindrical bore whole body MR system, assessed using a GE Signa HDx whole body active shield MR scanner with software version 14/LX/MR and a phantom designed to simulate human tissue. The phantom average SAR calculated using calorimetry was 2.9 W/kg and local background SAR at the site of the implant was 8.4 W/kg.

The image artifact extended as far as 15mm from the implant for spin echo images and 40mm for gradient images when scanned in non-clinical testing in a 3.0T GE signa HDx MR system. The implant has not been evaluated in MR systems other than 1.5 or 3.0T.

Medtronic CoreValve® Family of THV (Including Evolut R and Evolut Pro)

Medtronic CoreValve LLC

1.5 Tesla

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[1] Information ascertained from manufacturer's Instructions For Use (IFU) available in the public domain as of 03 November 2011. Precautions for specific devices should always be referenced using the manufacturer's current IFU.

[2] Edwards Lifesciences LLC, Web IFU 199473001A
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM262938.pdf

Based on non-clinical testing and modeling, a 26 mm bioprosthesis was calculated to produce a temperature rise of less than 3.5°C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR scanning in a 64 MHz whole body transmit coil, which corresponds to a static field of 1.5 Tesla.

3.0 Tesla

Based on non-clinical testing and modeling, a 26 mm bioprosthesis was calculated to produce a temperature rise of less than 3.6°C at a maximum whole body averaged specific absorption rate (SAR) of 2.0 W/kg for 15 minutes of MR scanning in a 128 MHz whole body transmit coil, which corresponds to a static field of 3.0 Tesla.

1.5 and 3.0 Tesla

The bioprosthesis should not move or migrate when exposed to MR scanning immediately after implantation. MRI of at least 3 tesla and 1.5 tesla may be performed immediately following the implantation of the bioprosthesis. The magnetic force on the bioprosthesis- determined at a location where the magnitude of the magnetic field strength was about 1.5 tesla and the magnitude of the spatial gradient of the magnetic field was about 400 gauss/cm – was determined to be less than 5% of its weight. Non-clinical testing at field strengths other than 1.5 tesla and 3.0 tesla has not been performed to evaluate bioprosthesis heating.

MR image quality may be compromised if the area of interest is in the same area, or relatively close to the position of the device. It may be necessary to optimize the MR imaging parameters for the presence of the implant. When tested at 3.0 tesla, the image artifact extended less than 3 mm beyond the bioprosthesis for the spin echo sequence with TR = 500 ms and TE = 20 ms and less than 7 mm beyond the bioprosthesis for the gradient echo sequence with TR = 100 ms and TE = 14.4 ms and flip angle = 30°. The mid region of the device lumen was obscured.

16.10 Appendix X: CT Angiography Imaging Acquisition Guidelines

The REFLECT Trial
Computed Tomography (CT) Angiography Acquisition Guidelines

Table of Contents

1.0 **Background**

Cardiac Multi-Detector Computed Tomographic Angiography (Cardiac MDCT Angiography) is intended to evaluate aortic valve anatomy, aortic root dimensions for prosthetic valve sizing, and assessment of the aorta and peripheral vessels for anatomy and disease burden. The CT scan results will be used for assessment of the aortic arch for compliance with positioning of Keystone Heart TriGuard™ as well as planning the best fluoroscopy angle for the procedure. Assessment of the ileo-femoral arteries will indicate if the peripheral arteries anatomy can accommodate the TriGuard delivery system.

2.0 **Equipment**

- Multi-detector CT scanner (64-slice minimum) with ECG-gating capability.
    - The scans submitted for analysis of the aortic root should be ECG-gated; non-gated scans in areas with cardiac motion lead to measurement inaccuracy and therefore incomplete information for device selection.
    - Abdominal aorta and peripheral vessel image acquisition may be non-gated.
- Dual-source scanner preferred due to enhanced temporal resolution and reduced motion artifacts.

3.0 **Scans**

1) Chest Topogram.
2) Prospective ECG-gated non-contrast scan of aortic root and thoracic aorta.
3) Retrospective ECG-gated contrast enhanced scan of the aortic root and thoracic aorta, immediately followed by non ECG-gated contrast enhanced scan of the abdominal aorta and peripheral vessels.*

*If CT scanner is incapable of sequential ECG-gated to non-ECG gated scan, the contrast enhanced CT study can be performed using retrospective ECG-gating in its entirety.

4.0 **Scanning Procedures**

The optimal scan is similar to a coronary calcium score scan followed by a CT coronary angiogram / aortogram. The aim is to first evaluate the degree of calcification in the aortic valve, and then to obtain adequate contrast in the following regions of interest: endo-luminal surface for visualization of left heart, aorta, and peripheral access vessels (i.e., femoral arteries). Temporal resolution should be optimized to reduce motion artifact. Spatial resolution should be as high as possible (goal is smallest isotropic voxel size).

4.1 Step 1: Patient Preparation

- Administer medication per institution standard practice for CT scanning.
- Attach ECG electrodes for gating of scan. Verify quality of ECG tracing on scanner console.
- Prepare intravenous line for administration of contrast media.
- Assess heart rate variability during breath-hold.

4.2 Step 2: Chest Topogram

- A chest topogram can be used to plan subsequent imaging.

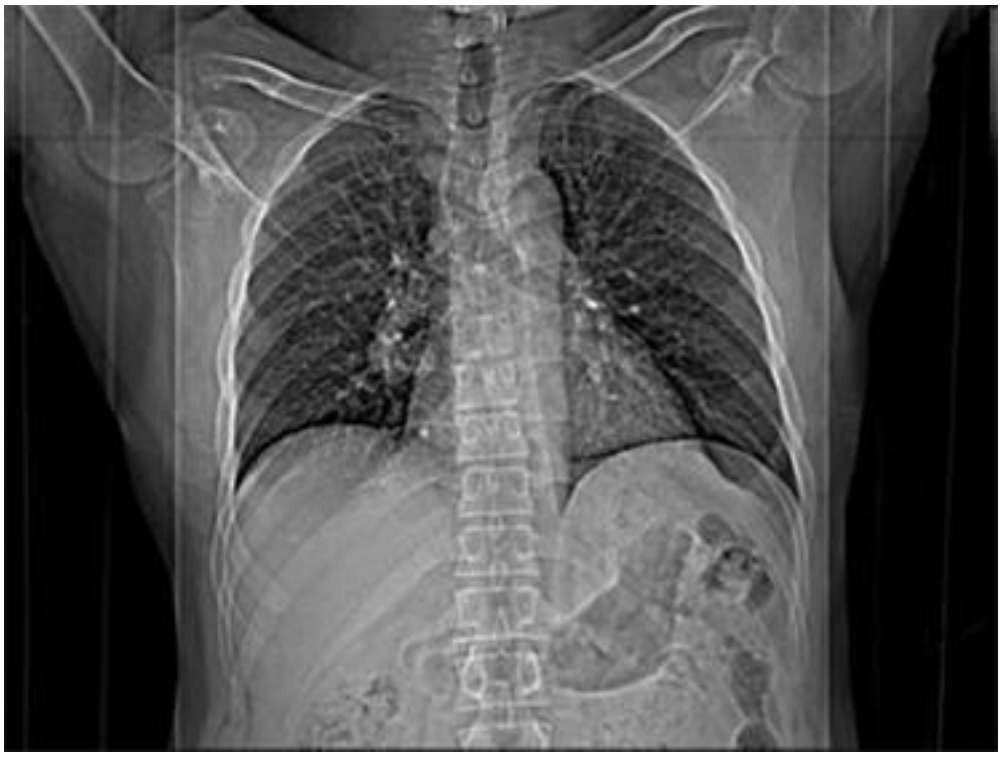


Figure CTA-1: Example image of chest topogram

4.3 Step 3: Prospective ECG-gated non-contrast scan of aortic root

The aim of this scan is to quantify the extent of calcium in the aortic valve and aorta, equivalent to scans calculating a coronary calcium score (e.g. Agatston score).

1. The submitted scan should cover the area from the temporal-mandibular-joint (TMJ) to the diaphragm to encompass the entire heart, aortic arch and thoracic aorta.
2. Prospective ECG-gating with sequential slice acquisition is preferred.
3. Scan at peak voltage of 120kVp with tube current of 140-150 mAs tube current.
4. Slice thickness 2.5-3.0 mm with a pitch of 1.

4.4 Step 4: ECG-gated contrast enhanced scan of the aortic root and thoracic aorta, and non-ECG gated contrast enhanced scan of abdominal aorta and peripheral vessels

The aim of this scan is to assess the anatomy of the aortic root, aortic arch and cerebral vessels, thoracic / abdominal aorta, and peripheral vessels (please refer to Table 1 below for suggested parameters).

1. The optimal scan would include the area from the temporal-mandibular-joint (TMJ) to the mid-thigh, using dynamic 4D acquisition and retrospective ECG-gating from the TMJ to the diaphragm (to evaluate the aortic root, aortic arch, cerebral vessels and thoracic aorta), followed by a non-ECG-gated scan from the diaphragm to the mid-thigh (to evaluate the abdominal aorta and peripheral vessels). If a sequential ECG-gated/non-ECG gated study is not available, the entire study could be performed using retrospective ECG-gating.
2. Detector collimation is 0.4-0.625mm.
3. Slice thickness is ≤ 0.8mm.
4. Peak voltage of 120kVp with tube current from 350-550 mAs per scanner protocol for patient body mass index.

4.4.1 Example Contrast Enhanced Scan Acquisition Procedure

- Prepare iodinated contrast injection apparatus (suggested scan parameters are provided in Table 1).
- Ensure availability of immediate treatments in case of contrast allergy.
- Set up scan parameters.
- Instruct patient to lie still during scan, even if they experience warmth or tingling due to the injection of contrast.
- Initiate contrast injection.
- When contrast reaches threshold at bolus-tracking location, instruct patient to hold breath at end-inspiration, then initiate main scan.
- At completion of scan, verify scan is of adequate quality.
- Record amount of contrast given.
- Record heart rate average and range.
- Record dose-length-product

4.4.2 Example Post-processing Procedure

- Verify heart rate ECG triggers are at consistent place in cardiac cycle, edit if necessary. Additional editing/removal of arrhythmias may be performed.
- Reconstruct at multiple phases (20 preferred, increments of 5-10%), with ≤0.8mm slice thickness. If the system has the capability, also reconstruct a “best systolic” and “best diastolic” phase.

4.5 Step 5: Submission of CT data

All available CT data should be sent electronically to the data center (Core Laboratory).

- Data should be stored in DICOM 3.0 format, not DICOMDAT.
- Submitted images must have patient identifiers (protected health information (PHI) such as name, date of birth, medical record number) removed at time of image transfer to the data center.
- Please use the following during anonymization:

- **Modality** = CT
- **“Body Part Examined” contains the value** = CHEST
- **“Protocol Name” contains any of the values** = PWI, Brain, Neuro, Perf, Low Grade
- **“Series Description” contains any of the values** = CHEST TOPOGRAM, ECG NON CONTRAST AORTIC ROOT, ECG CONTRAST AORTIC ROOT, ECG CONTRAST THORATIC AORTA, NON ECG CONTRAST ABDOMINAL AORTA NON ECG CONTRAST PERIPHERAL VESSELS.

- Submitted imaging studies should be labeled as follows: **CCSCTC-SNR**

  CC- is the region ID which will be assigned in two letter format (US or UK).

  SC- is the site ID which will be assigned in two number format (01, 02, etc.).

  TC- is the internal ID which will be assigned in two number format (for REFLECT the number is 09).

  SNR- is the subject number which will be assigned in three number format (001, 002, etc.)

- Please provide all the following images if available:
  - Chest Topogram
  - ECG-gated non-contrast scan of aortic root and aortic arch
  - ECG-gated contrast enhanced scan of aortic root and thoracic aorta, immediately followed by non-ECG-gated contrast scan of abdominal aorta and peripheral vessels

Instructions for submission of CT imaging data will be reviewed with each site during CT Protocol Training sessions. Images will be sent via electronic transfer using the transfer solution.

Instructions will be provided during site set-up. Reference the transfer solutions Site User Guide and/or the Quick Reference Sheet for specific instructions regarding the electronic transfer of CT images.

Table 1. Suggested Scan Parameters for contrast enhanced scan of aortic root, aorta and peripheral vessels

	Dual-Source CT	**Single-Source CT**
IV injection with iodine contrast	100-120 (320 mg/ml or higher)	
Injection Rate	4-5 mL/s	
Bolus tracking, delay	Delay time calculated using protocol for current scanner (bolus tracking, etc.) with triggered by contrast concentration >100 HU in the high descending aorta	
ECG Leads	Required	
ECG-gating	Retrospective ECG-gating from TMJ to diaphragm; then non-ECG-gating from diaphragm to mid-thigh	
Scan direction	Cranial-caudal	
Scan coverage	From above the temporal mandibular joint to the mid-thigh	
Detector collimation	0.4-0.625 mm	
Pitch	0.2-0.43 adapted to the heart rate	0.2 adapted to heart rate
Dose modulation	Modulation between 30% and 80% of the cardiac cycle	
Slice thickness	0.8mm	
Slice overlap	0.4mm	
Reconstruction kernel	B25 Smooth++	Medium Smooth
Post-processing	Use retrospective ECG gating reconstruction algorithm that minimizes motion artifact. Reconstruct at multiple phases (20 preferred, increments of 5-10%). Reconstructed slice thickness 0.4-0.6 mm.	

16.11 Appendix XI: SF-36 Health Survey

The Short Form Short Form 36 Health Survey (SF-36v2) is copyright Medical Outcomes Trust and Quality Metric Incorporated, and is licensed for use in this trial; authorized copies, alternate versions, and translations will be provided as required. A sample form is provided below for informational purposes.

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. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. 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>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

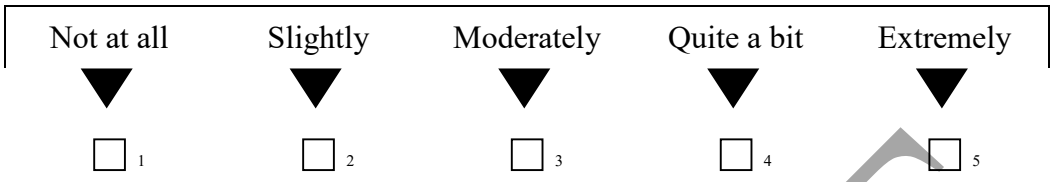
4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

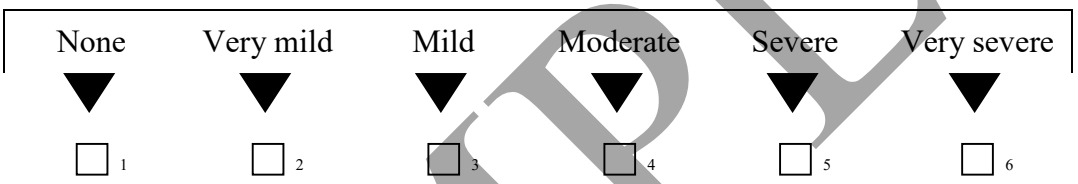
5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

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

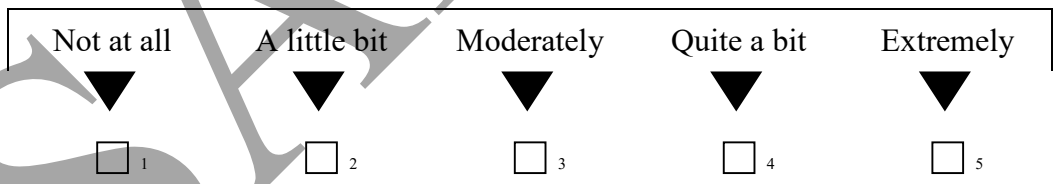
6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past week</u>?



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



9. These questions are about how you feel and how things have been with you <u>during the past week</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 week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with 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

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	1	2	3	4	5
b	I am as healthy as anybody I know	1	2	3	4	5
c	I expect my health to get worse	1	2	3	4	5
d	My health is excellent	1	2	3	4	5

Thank you for completing these questions!