SUPPLEMENTARY APPENDICES

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Appendix 2

Vascular Graft Solutions Ltd.

Protocol number	CD0131
Study title	A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support
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VEST Manufacturer	Vascular Graft Solutions Ltd. (VGS) 24 Raoul Wallenberg St. Tel Aviv, Israel 6971921 Tel: +972-3-5499054 Fax: +972-3-6024966
Sponsor Contact	Orit Yarden, PhD Mobile: +972-54-3073050 orit@graftsolutions.com
Clinical and Data Coordinating Center (DCC)	International Center for Health Outcomes and Innovation Research (InCHOIR) Coordinating Center for the Cardiothoracic Surgical Trials Network (CTSN) Icahn School of Medicine at Mount Sinai New York

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Sponsor in confidence and.

I have read this protocol in its entirety and I agree to all aspects.

_____	_____
Investigator printed name	Site
_____	_____
Signature	Date

RETURN TO SPONSOR WITH THE ATTACHED PROTOCOL

CONTENTS

Definitions, Acronyms & Abbreviations

21CFR	Code of Federal Regulation number 21
AE	Adverse event
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
CFR	Coronary Flow reserve
CV	Coefficient variance
CT	Computed tomography
CTSN	Cardiothoracic Surgical Trials Network
Cr	Creatinine
CRF	Case report form
cTn	Cardiac troponin
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
FDA	Food and Drug Administration
FFR	Fractional Flow reserve
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IABP	Intra-aortic balloon pump
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IFU	Instructions for use
IRB	Institutional Review Board
IVUS	Intra vascular ultrasound
LAD	Left anterior descending coronary artery
LBBB	Left bundle branch block
LIMA	Left internal mammary artery
LOS	Length of stay
iMA	Internal mammary artery
MACCE	Major adverse cardiac and cerebrovascular events
MI	Myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NP	Nurse Practitioner
PA	Physician's Assistant
PCI	Percutaneous coronary intervention
PI	Pulsatility index
PMA	Premarket approval
SAE	Serious adverse event
SMC	Smooth muscle cell
SOC	Standard of care
SOP	Standard operating procedure
SVG	Saphenous vein graft
QCA	Quantitative coronary angiography
TIMI	Thrombolysis in myocardial infarction
TTFM	Transit time flow measurement
UADE	Unanticipated adverse device effect
URL	Upper reference limit
VEST	Venous external support
VGS	Vascular Graft Solutions Ltd.

Synopsis

STUDY TITLE	A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support
STUDY	VEST™ Venous External Support
TREATMENT PHASE	Pivotal study under an Investigational Device Exemption (IDE) Primary endpoints at 12 months will be used to support a PMA application. Long term data, up to 5 years follow-up, will be monitored in the post-approval period.
CLINICAL SIGNIFICANCE	Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease. Despite the proposed benefits of multiple arterial grafts, autologous saphenous vein grafts (SVGs) are still the most frequently used bypass conduits in CABG. Progressive SVG failure after CABG remains a key limitation to the long-term success of surgery.
OBJECTIVES	To demonstrate the safety and effectiveness of the VEST for its intended use: Limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease.
STUDY DESIGN	Prospective, multi-center, randomized, within-subject-controlled , trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison between two sets of SVGs: A VEST supported set; and an unsupported set.
ENDPOINTS	Primary endpoint: Intimal hyperplasia (plaque+media) area [mm^2] as assessed by IVUS at 12 months. Occluded vessels are accounted for in the analysis of the primary endpoint. Secondary confirmatory endpoints: 1. Lumen diameter uniformity, assessed by angiography for each graft separately and expressed by the Fitzgibbon classification (22), on a 3-point ordinal scale: I – No intimal irregularity II – Irregularity of <50% of estimated intimal surface III – Irregularity of >50% of estimated intimal surface 2. Graft Failure (≥50% stenosis) by cardiac angiography at 12 months Clinical Events 1. Serious adverse events 2. MACCE 3. Mortality 4. Hospitalization
RX ARMS	In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Patients will be block randomized in two stages: Stage 1: Assign either right or left grafts to receive the VEST device Stage 2: If in Stage 1 the right vein graft was chosen to receive the VEST, Stage 2 will randomly assign one of the left vein grafts to control (if there is only one left vein graft, it will be assigned to control)

If in Stage 1 the left side was chosen, Stage 2 will randomly assign one left vein graft to treatment (if there is only one left vein graft, it will be assigned to treatment)

COHORT

Sample size
224 subjects will be enrolled in this trial.

Inclusion criteria

1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation.
2. Age 21 years or older.
3. Planned and scheduled on-pump CABG.
4. Two or more vein grafts: 1 for the right coronary artery, 1 or more for the left coronary arteries, with native vessels having at least 75% stenosis.
5. IMA graft indicated for the LAD and additional arterial graft considered based on practice guidelines. A patient who is candidate for one, two, or more arterial grafts would only be eligible if in addition to the arterial grafts at least two vein grafts are used as specified above.
6. Appropriately sized and accessible target coronary arteries, with a minimum diameter of 1.5 mm and adequate vascular bed (without significant distal stenosis), as assessed by pre-operative cardiac angiography.

Exclusion criteria

1. Concomitant non-CABG cardiac surgical procedure.
2. Prior cardiac surgery.
3. Emergency CABG surgery (cardiogenic shock, inotropic pressure support, IABP).
4. Contraindication for on-pump CABG with cardioplegic arrest (e.g., severely calcified aorta).
5. Calcification at the intended anastomotic sites, as assessed upon opening of the chest and before randomization.
6. Severe vein varicosity as assessed after vein harvesting and before randomization.
7. History of clinical stroke within 3 months prior to randomization.
8. Severe renal dysfunction (Cr>2.0 mg/dL).
9. Documented or suspected untreated diffuse peripheral vascular disease such as: carotid stenosis or claudication of the extremities.
10. Concomitant life-threatening disease likely to limit life expectancy to less than two years.
11. Inability to tolerate or comply with required guideline-based post-operative drug regimen (antiplatelet plus statin) and/or inability to take aspirin.
12. Inability to comply with required follow-ups including angiographic imaging methods (e.g. contrast allergy).
13. Concurrent participation in an interventional (drug or device) trial.

DATA AND SAFETY MONITORING

An independent Data and Safety Monitoring Board (DSMB) will oversee patient safety and overall progress of the study. An independent Event Adjudication Committee (EAC) will review and adjudicate adverse events occurring during this trial. Stopping guidelines for safety will be developed based upon trial data.

DURATION

Accrual is expected to take 12 months, and all patients will be followed for the primary endpoint at 1 year post-randomization, with annual visits until 5 years post-randomization

Data Collection Schedule

Assessment	Screening/ Baseline	Intra-Op	6 Weeks	6 Months	12 Months	Years 2,3,4,5
General						
Informed Consent	X					
Release of Medical Information	X					
Screening Log and Registration	X					
Medical History	X					
Laboratory Assessment	X					
Medications	X		X	X	X	X
Physical Exam	X				X	
ECG	X		X	X	X	X
Coronary Angiography	X				X	
Eligibility Criteria	X					
Intravascular Ultrasound					X	
Randomization		X				
Surgical Procedure		X				
Event Driven Data						
Serious Adverse Events		X	X	X	X	
MACCE		X	X	X	X	X
Hospitalization	X	X	X	X	X	X

1. Objectives

The purpose of this study is to demonstrate the safety and effectiveness of the VEST for its intended use: limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting (CABG) procedures as treatment for coronary arteriosclerotic disease.

This protocol describes a prospective, multi-center, randomized, within-subject-controlled, open label clinical trial to evaluate the safety and effectiveness of the VEST, an external mechanical support for autologous saphenous vein grafts that are created during Coronary Artery Bypass Surgery (CABG).

This study is designed to provide safety and effectiveness data with co-primary endpoints measured over 12 month follow up post index CABG procedure. Patients will continue to be followed annually up to 5 years in the post-approval period.

2. Background and Rationale

2.1 The Clinical Need

Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease (1). Despite the proposed benefits of multiple arterial grafts (2), autologous saphenous vein grafts (SVGs) are still, numerically, the most frequently used bypass conduits in CABG. However, progressive SVG failure after CABG remains a key limitation to the long-term success of surgery (3, 4). As many as 25% of SVGs occlude within 1 year of CABG; an additional 1-2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which are disease free (5).

Intimal hyperplasia and subsequent SVG failure have significant effects on clinical outcomes such as onset of angina, need for revascularization intervention (surgical or percutaneous), myocardial infarction (MI), and death. The localized areas of "adaptive" intimal hyperplasia that occur in native human arteries have been defined by the American Heart Association Council on Arteriosclerosis as "atherosclerosis-prone regions" (6). FDA recognizes mitigation of intimal hyperplasia as the main effect mode of the drugs eluted by coronary stents (7). In a similar process the extensive intimal hyperplasia throughout the length of a vein graft may effectively create a diffuse atherosclerosis-prone region (4).

The pathophysiology of SVG failure is a well-documented consequence of several intrinsic and extrinsic factors (3, 4). Beyond short-term factors and technical surgical errors, stenosis and failure is dominated by proliferation of intimal hyperplasia which is the foundation for graft atheroma and subsequent vein graft failure, ultimately resulting in higher rates of coronary re-intervention (stenting or re-do CABG), stroke, MI and death in patients with failed SVGs.

Several factors contribute to SVG failure in the short term. Even under optimal conditions, saphenous vein harvesting results in endothelial cell loss, damage to medial smooth muscle cells (SMC), and disruption of micro-perfusion to the vessel wall (10).

Following implantation into a vigorous arterial circulation system, saphenous veins may experience abrupt hemodynamic changes with increased blood pressure, shear stress, wall tension, and pulsatile flow (11,12,13). Among these, high circumferential wall stress and low wall shear stress coupled with intraluminal irregularities are the dominant promoters of vein grafts stenosis (14,15).

Evidence from experimental studies has indicated a strong causal relationship between increased circumferential wall stress and activation of various intracellular signaling molecules (15). These chains of events stimulate vascular smooth muscle cells proliferation and migration in the media, accelerating the progression of intimal hyperplasia. From the standpoint of hemodynamic adaptation, the ratio of lumen radius to wall thickness in vein grafts tends to approach the same value as that in run-off arteries for maximum efficiency of blood transportation. Accordingly, structural remodeling of the venous lumen and wall occurs (13). An external vein graft support has the ability to limit abrupt dilatation and associated wall

stretch, reinforce the venous wall thus absorbing pressure, and subsequently mitigate and suppress the proliferative reaction induced by high wall stress.

In addition to significant effects on the vein graft wall, the arterialization of the vein graft results in disturbed and turbulent flow patterns within the vein grafts. The irregular remodeling and dilatation result in a non-uniform lumen which in turn results in disturbed turbulent and oscillatory flow which in turn promote atherogenesis (16). The geometric diameter mismatch between artery and vein also results in flow discrepancies (13,14). An external vein graft support such as the VEST is designed to regulate flow patterns by enhancing lumen uniformity.

Over the longer term, proliferation of intimal hyperplasia renders the vein graft lumen vulnerable to atherosclerosis leading to SVG stenosis and occlusion (17,18,19,20,21).

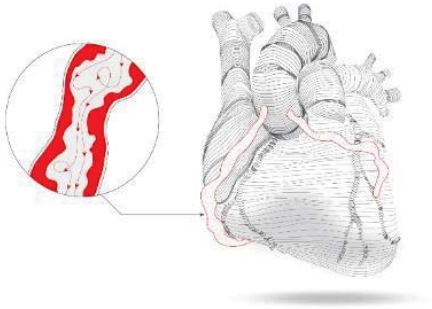

Figure 1: Vein graft remodeling flow disturbances

2.2 Perivascular External Support

Attempts to mitigate intimal hyperplasia and SVG failure have been the focus of intense clinical research. Pharmacological attempts, including Edifoligide (8) and aspirin + clopidogrel (9), have both failed to reduce SVG failure or mitigate intimal hyperplasia, respectively at 12-18, months after CABG.

Mechanical external supports for SVGs have shown considerable promise in pre-clinical testing with reduction of vessel dilatation and stretch, proliferative intimal hyperplasia and medial thickening (24, 25, 26, 27, 28). External support also reduces the diameter mismatch between the vein graft and the host coronary artery and increases the lumen uniformity (29). Furthermore, external stents have been shown to facilitate adventitial neovascularization that counteracts damage to the vein graft's vasa vasorum during harvesting (30, 31). However, limited clinical data has been published to date with such devices and adoption into clinical practice is lacking. In two randomized self-controlled studies of other devices intended to provide permanent support to SVGs, Murphy et al (32) describe 100% occlusion of supported SVGs at six months and Schoettler et al (33) report a 72% occlusion rate at nine months. Both these external stents (Figure 2) required gluing and/or suturing to the vein graft in order to optimize length and diameter match and to prevent migration, which may explain their lack of success.

The eSVS Mesh described in Schoettler et al (33) requires both application of fibrin glue and suturing the anastomoses through the device mesh. The anastomoses are probably the most sensitive part of the CABG procedure and are the most prone to technical errors. In addition, the application of fibrin glue on vein grafts has been tested in-vivo in a porcine model and has been histologically shown to induce an increase of graft thickening (34) and may contribute to vein graft failure (33). This is of course counterproductive to the attempts of external support devices to inhibit graft remodeling.

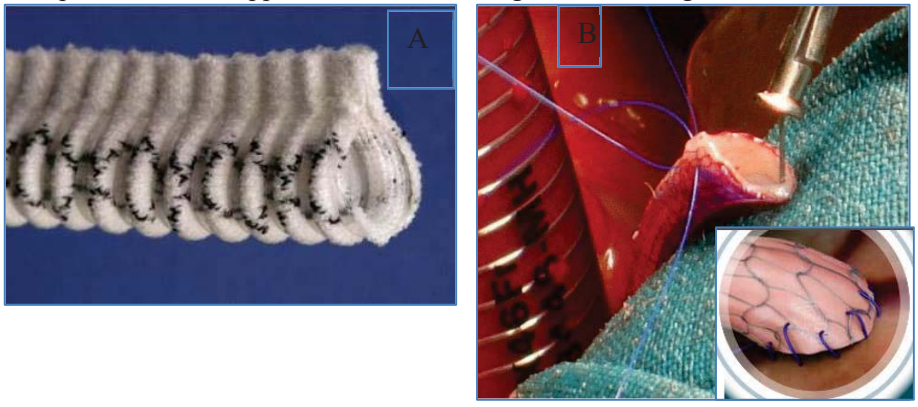

Figure 2: A: Extent external support (Schoettler et al); B: eSVS MEsh esternal support (Murphy et al)

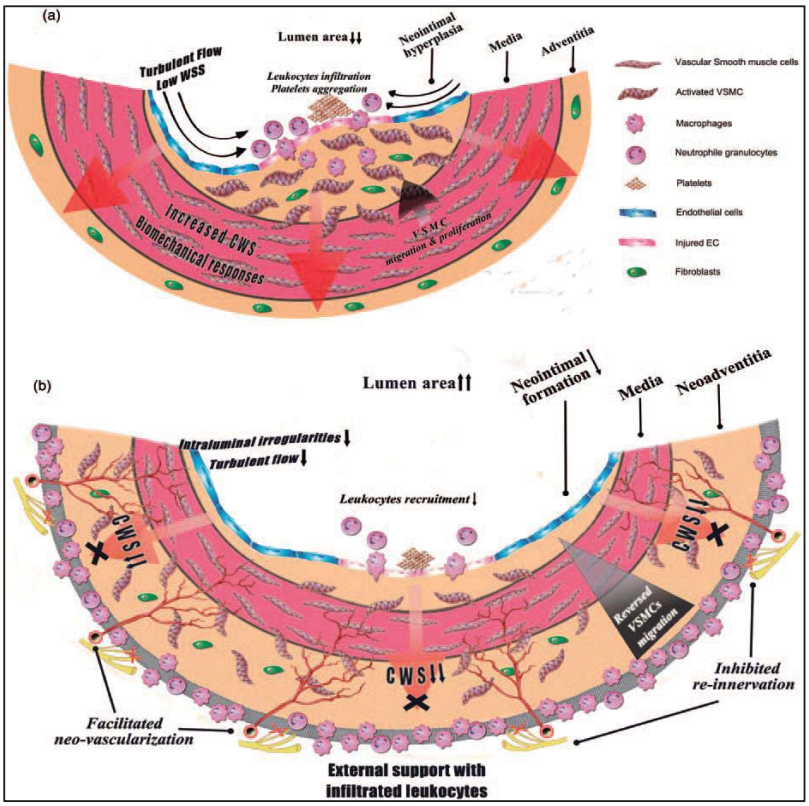

Figure 3: (Adapted from Hu & Wan (13)): Schematic diagram illustrating the pathogenesis of venous wall over-thickening and the mechanisms involved in external stenting of the vein graft: (a) failure of unsupported vein grafts due to neointimal hyperplasia and incorporated atherogenesis; (b) external prostheses preventing the venous wall from abrupt biomechanical changes through perivascular mechanical support, redirecting smooth muscle cell migration, facilitating neo-adventitial revascularization, and inhibiting re-innervation. CWS: circumferential wall stress; EC: endothelial cells; VSMC: vascular smooth muscle cells; WSS: wall shear stress

Table 1: Processes of intimal hyperplasia formation and the respective external support mechanisms of action

Intimal hyperplasia proliferation mode	External support potential inhibitory effect (13)
Wall stretch and activation of signaling molecules triggering proliferation and migration of smooth muscle cells.	An external support enables external reinforcement, limits abrupt dilatation and thus minimizes the wall stretch trigger
Remodeling of the vein graft directed at achieving arterial wall thickness to lumen radius ratio causes lumen irregularities.	An external support inhibits remodeling and promotes lumen uniformity
Turbulent and oscillatory flow caused by lumen irregularity adversely affects the blood-endothelial interface, activating smooth muscle cells and platelet aggregation.	An external support maintains lumen uniformity, hence inhibits turbulence and flow oscillations.
Dysfunction of vascular vasa-vasorum due to the harvesting procedure causes migration of smooth muscle cells and fibroblasts towards the inner layer, oxygenating by the oxygen rich arterial circulation.	An external support triggers growth of neo-adventitial vasculature which supplies the venous wall and inhibits inward migration of smooth muscle cells.
Inward migration of smooth muscle cells	An external support causes foreign body reaction which promotes outward redirection of the migration of smooth muscle cells and fibroblasts (accumulating around the external support) instead of migrating inwards.

2.3 The VEST

VEST (Venous External Support) manufactured by Vascular Graft Solutions Ltd, is an external mechanical support for autologous saphenous vein grafts that are created during Coronary Artery Bypass Surgery (CABG). The VEST (Figure 4, Figure 5) is deployed over the vein graft by the cardiac surgeon during the CABG procedure in a simple user-friendly manner. The implantation process takes only 1 minute and does not add any significant time to the overall CABG duration. The VEST does not require attachment to the vein graft or to the anastomoses by any external means (sutures or glue).

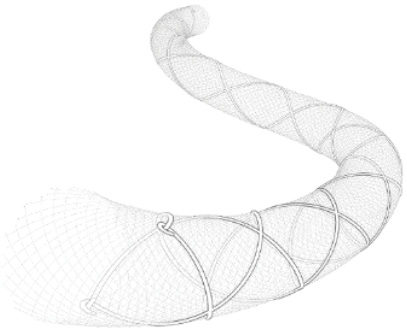

Figure 4: The VEST

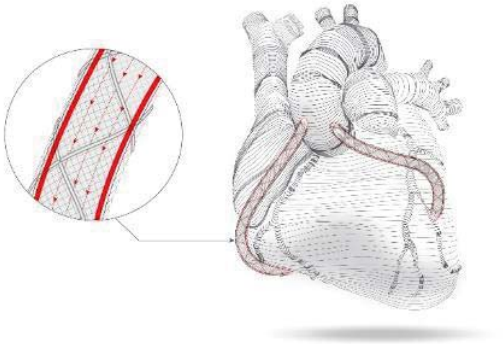

Figure 5: Two VESTs deployed over SVGs

The VEST is designed to target the underlying factors leading to SVG disease progression and, in particular, proliferation of intimal hyperplasia. Several effect modes are combined to deliver the desired effect:

- Prevention of post implantation dilatation
- Restraining wall tension
- Prevention of graft ectasia (segmental dilatation)
- Mitigation of occlusive thrombosis
- Enhancing diameter match with coronary artery
- Maintaining lumen uniformity
- Improving flow patterns

2.3.1. Intended Use

The VEST is indicated for use in limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease. Information on product design and accessories is available in the device Instructions for Use.

3. Overall Study Design

3.1 Structure

This is a prospective, multi-center, randomized, within-subject-controlled trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison of the co-primary effectiveness endpoint between two sets of SVGs: A VEST-supported set; and a non-supported set. While the primary endpoint is assessed at 12 months post randomization, patient follow-up will continue for 5 years in order to demonstrate long-term outcomes of the VEST.

3.2 Rationale for Primary Endpoint

The primary endpoint is the degree of intimal hyperplasia at one year as assessed by IVUS. Missing IVUS data due to vessel occlusion will be imputed using a non-ignorable mechanism (not missing at random). The rationale for analyzing this endpoint in this manner is that it reflects efficacy in reducing intimal hyperplasia and does not exclude occluded vessels, which are a safety concern. Proliferation of intimal hyperplasia is an ongoing process over years post CABG. The presumed efficacy of the VEST is its ability to slow down the rate of intimal hyperplasia formation. This study is designed to evaluate the difference between intimal hyperplasia area of VEST supported and unsupported vein grafts at one year after randomization. The within-subject design has advantages in that it reduces between-treatment variability by having each patient serve as their own control, but affects the ability to attribute serious adverse events to a treatment. We will capture serious adverse events in this trial, including MACCE.

3.3 Randomization

For every patient, a pair of grafts will be designated for participation in the trial; one to be supported with the VEST device and the other to serve as a control. Grafts to the LAD do not participate in the randomization.

Patients will be block randomized in two stages:

- Stage 1: Assign either right or left grafts to receive the VEST device
- Stage 2:
    - If in Stage 1 the right vein graft was chosen to receive the VEST, Stage 2 will randomly assign one of the left vein grafts to control (if there is only one left vein graft, it will be assigned to control)
    - If in Stage 1 the left side was chosen, Stage 2 will randomly assign one left vein graft to treatment (if there is only one left vein graft, it will be assigned to treatment).

Only grafts originating proximally from the aorta will be considered for randomization. ***Sequential grafts will not be included in the study.*** In the left territory, where more than one graft may be performed, the vein grafts will be uniquely distinguished by their pre-measured length as “Longest Left” and “Shortest Left”. This design will allow for within-subject comparisons, which is expected to increase power relative to a between-subject design.

To prevent any bias as well as exclude any ineligible patients, randomization will be performed only after the procedure has reached the stage where all venous bypass distal anastomoses have been constructed.

3.4 Masking

The nature of the study precludes masking surgeons from treatment assignment. In order to prevent selection bias, randomization into treatment assignment is performed intraoperatively only after all distal anastomoses have been completed (see section 6.2). Investigators will also be blinded to all data from other clinical sites, as well as the primary outcomes data and aggregate data regarding clinical outcome. Serious unexpected AEs will be reported to Institutional Review Board (IRB) as usual. Clinical events including serious and protocol-defined adverse events will be reviewed by an Event Adjudication Committee. All angiograms and intimal hyperplasia scoring will be analyzed, according to predefined analysis protocols, by independent core laboratory personnel who will be blinded to clinical outcomes.

4. Study Population

4.1 Number of Patients

A total of 224 subjects will be enrolled in up to 20 US and Canadian sites.

4.2 Eligibility Criteria

4.2.1. Inclusion Criteria

Eligible patients will meet all the following inclusion criteria:

1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation.
2. Age 21 years or older.
3. Planned and scheduled on-pump CABG.

4. Two or more vein grafts: 1 for the right coronary artery, 1 or more for the left coronary arteries, with native vessels having at least 75% stenosis.
5. IMA graft indicated for the LAD and additional arterial graft considered based on practice guidelines. A patient who is a candidate for one, two, or more arterial grafts would only be eligible if in addition to the arterial grafts at least two vein grafts are used as specified above.
6. Appropriately sized and accessible target coronary arteries, with a minimum diameter of 1.5 mm and adequate vascular bed (without significant distal stenosis), as assessed by pre-operative cardiac angiography.

4.2.2. Exclusion Criteria

Patients will be excluded if they meet any of the following:

1. Concomitant non-CABG cardiac procedure.
2. Prior cardiac surgery.
3. Emergency CABG surgery (cardiogenic shock, inotropic pressure support, IABP).
4. Contraindication for on-pump CABG with cardioplegic arrest (e.g. severely calcified aorta).
5. Calcification at the intended anastomotic sites, as assessed upon opening of the chest and before randomization.
6. Severe vein varicosity as assessed after vein harvesting and before randomization.
7. History of clinical stroke within 3 months prior to randomization.
8. Severe renal dysfunction (Cr>2.0 mg/dL).
9. Documented or suspected untreated diffuse peripheral vascular disease such as: carotid stenosis or claudication of the extremities.
10. Concomitant life-threatening disease likely to limit life expectancy to less than two years.
11. Inability to tolerate or comply with required guideline-based post-operative drug regimen (antiplatelet plus statin) and/or inability to take aspirin.
12. Inability to comply with required follow-ups including angiographic imaging methods (e.g. contrast allergy).
13. Concurrent participation in an interventional (drug or device) trial.

4.3 Recruitment Strategies

CABG is a prevalent cardiac surgical procedure conducted within the participating Cardiothoracic Surgical Trials Network (CTSN) centers. We will establish enrollment targets for each clinical site based on a review of pre-screening logs. Enrollment strategies may include mailings to referring physicians of the study hospitals, symposia, and health care events targeted towards this population as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified accrual goals, and additional interventions to facilitate enrollment will be implemented as needed. The Pre-Screening Failure Log will identify numbers of patients screened and reasons for ineligibility and/or non-enrollment into the trial.

4.4 Inclusion of Women and Minorities

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

- Documentation of the number of women and minorities screened and enrolled via screening and pre-screening failure logs;
- Monitoring of such logs from each clinical center on a regular basis;
- If necessary, develop and implement outreach programs designed to recruit adequate numbers of women or minorities.

4.5 Relevance to Medicare beneficiaries

The cohort eligible for participation in this study are all patients with multivessel coronary artery disease scheduled to undergo CABG procedure. From the literature (1,8) we know that CABG patients are typically with a median age of 64-65 years. Hence it is expected that approximately half the patients will be Medicare beneficiaries.

5. Definitions and Measurements of Endpoints and Outcomes

5.1 Primary Endpoint

The primary endpoint is defined as intimal hyperplasia (plaque+media) area [mm^2] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (VEST supported and unsupported) and is measured as a continuous variable.

5.2 Secondary Confirmatory Endpoints

1. *Lumen diameter uniformity* will be assessed by angiography for each graft separately and expressed by the Fitzgibbon classification (22), on a 3-point ordinal scale:
   - I – No intimal irregularity
   - II – Irregularity of <50% of estimated intimal surface
   - III – Irregularity of >50% of estimated intimal surface

2. *Graft Failure* coded as follows:

0 = Failure = ≥50% stenosis by QCA at 12 months
1 = Success = Otherwise

5.3 Additional Secondary Endpoints

- *Intimal hyperplasia:* (plaque + media) thickness [mm] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (supported and unsupported) and is measured as a continuous variable.
- *TIMI flow grade* assessed by angiography at 12 months on the following 4-point ordinal scale:
  - Grade 0 – No perfusion
  - Grade 1 – Penetration without perfusion
  - Grade 2 – Partial perfusion
  - Grade 3 – Complete perfusion
- *Graft failure* at 12 months, as defined above, separately for right and left territories
- *Repeat revascularization* for supported and unsupported vein grafts (or respective bypassed target coronary artery) over the 5 years of observation
- *Lumen diameter uniformity* expressed by the coefficient of variance (CV) by QCA at 12 months, computed for each graft separately and scored continuously as follows:

$CV_{Uniformity} = SD_{Diameter}/Mean_{Diameter}$

- *Ratio of vein graft lumen diameter to target artery lumen diameter* by QCA at 12 months

5.4 Clinical Events

- Mortality

All-cause mortality will be assessed.

- Hospitalizations
  - Length of Index Hospitalization

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

  - Readmissions

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

- Safety
  - Serious Adverse Events occurring post randomization and up to 12 months after the CABG procedure

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

- MACCE

Major adverse cardiac and cerebrovascular events (MACCE) occurring within 12 months and annually after up to 60 months after the index CABG procedure. MACCE is defined below.

  - All-cause **mortality**;
  - **Stroke** - Defined as any new, rapidly developing focal neurological deficit, lasting longer than 24 hours, ascertained by a standard neurological examination (administered by a neurologist or other

qualified physician and documented with appropriate diagnostic tests, imaging and neurology consultation note). The Modified Rankin Scale and the NIH Stroke Scale must be administered within 24 hours following the event to document the presence and severity of neurological deficits.

Each neurological event must be subcategorized as:

- Hemorrhagic stroke
- Ischemic stroke
- Other

- **Myocardial infarction (MI)** – Any one of the following criteria meets the diagnosis of MI
  - **Acute MI** - Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the Upper Reference Limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumably new significant ST-T changes or new LBBB;
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy
  - **CABG related MI** - defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either
  - New pathological Q waves or new LBBB, or
  - Angiographic documented new graft or new native coronary artery occlusion, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - **Prior MI** – Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence on non-ischemic cause.
  - Pathological finding of prior MI
- **Ischemic driven target vessel revascularization** - (CABG or PCI) of **VEST supported** vein graft or associated target coronary artery.

  Revascularization is considered ischemic driven if the subject has clinical or functional ischemia manifesting in any of the following:
  - **A history of angina pectoris** presumably related to the target vessel
  - **Objective signs of ischemia at rest** (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
  - **Abnormal results of any invasive functional diagnostic test** [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

  The angiography and IVUS procedure performed at 12 months to assess the graft integrity by the study plan will not be counted as MACCE. Clinical evaluation for the 12 months visit will be completed and MACCE will be recorded **prior to** performance of the planned interventional procedure. If revascularization of the VEST supported graft or associated bypassed coronary artery is performed as a result of the angiography, it will be reported and adjudicated according to the definition given above for ischemic driven target vessel revascularization, for assessment of MACCE at time points >12 months.

- *Time to revascularization* for supported and unsupported vein grafts (or respective bypassed target coronary artery). See above definition for revascularization.
- *Revascularization rate* for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years. See above definition for revascularization
- *Time to MI in culprit vessels*, for supported and unsupported vein grafts (or respective bypassed target coronary artery). See above definition for MI
- *Rate of MI culprit vessels*, for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years. See above for definition of MI.

5.5 Specific Adverse Event Definitions

The following complications and adverse events are documented in the literature (5,8) and expected to occur with CABG patients. For the purposes of the trial, these events will be reported when they meet the definition below *and* meet the following definition for serious:

Serious Adverse Event: Serious adverse events (SAEs) are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators or Sponsor. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Bleeding

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

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

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

Cardiac Arrhythmias

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

Cardiac arrhythmias are classified as follows:

- Cardiac arrest
- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
- Cardiac conduction abnormalities or sustained bradycardia requiring permanent pacemaker placement (includes all PPMs whether associated with a serious AE or not)

Pericardial Fluid Collection

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

Pleural Effusion

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

Pneumothorax

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

Hepatic Dysfunction

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

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

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

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

Major Infection
A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

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

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

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

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

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

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

Heart Failure
Signs of inadequate organ perfusion or congestion, or a syndrome of compromised exertional tolerance manifested by dyspnea or fatigue that requires

- intravenous therapy (diuretics, inotropic support, or vasodilators) and prolongs hospital stay in the judgment of the investigator, or
- introduction of intravenous therapy (diuretics, inotropic support, or vasodilators) at any point following discharge from the index hospitalization, or
- readmission for heart failure

Arterial Non-CNS Thromboembolism
An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

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

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

Revascularization procedure
Revascularizations procedures which occur during the investigation must be reported to Sponsor as soon as possible. Every procedure will be recorded on a Revascularization CRF and the event documented as an adverse event on an Adverse Event CRF.

Other
An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

5.6 Events that do not need to be reported

All above-listed protocol-defined events, serious and non-serious, should be reported, while only serious non-protocol defined (i.e. "other") adverse events should be reported. Common medical events (as determined by the investigator) such as colds, influenza, elective minor outpatient procedures such as colonoscopy, minor trauma and musculoskeletal discomforts do not need to be reported as adverse events unless they result in a hospital visit. Events related to pre-existing non-cardiac ailments such as arthritis, gout, gastrointestinal reflux disorder do not need to be reported as adverse events unless they result in a hospital visit.

6. Data Collection Procedures

6.1 Screening and Baseline

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

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

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

Release of Medical Information Form
Prior to screening data collection and protocol defined procedures
The patient must sign the Release of Medical Information form or institutional equivalent that authorizes release of medical records, including hospital costing data, to the study Sponsor, investigators and monitors.

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

Medical History
Within 7 days prior to randomization
This form captures the information pertaining to the medical history including but not limited to previous myocardial infarction, myocardial revascularization, stroke, and other comorbidities such as diabetes, hyperlipidemia, and peripheral vascular disease. Information regarding the current medical condition is also captured including but not limited to disposition at time of screening (outpatient, inpatient, ICU, etc.).

Laboratory Assessment
Within 10 days prior to randomization
Creatinine *(mg/dl)* value will be recorded.

Angiography
Within 3 months of randomization
Angiographic data must be available for every candidate patient to assess inclusion criteria. This form captures the date(s) of angiography and all coronary anatomy.

Medications
Within 30 days prior to randomization
This form captures all categories of medications (including but not limited to cardiovascular, analgesic and psychopharmacological medications) at one pre-operative time point.

Physical Examination
Within 30 days prior to randomization
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

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

A representative from the DCC will be available to discuss any questions regarding patient eligibility.

6.2 Randomization

The randomization procedure will be performed inside the OR after confirmation by the surgical team of the patient's eligibility to randomize and performed only after the procedure has reached the stage where all distal anastomoses of the venous grafts have been constructed, to minimize bias and the chance of a randomized patient not participating in the trial. Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system once the checklist of inclusion and exclusion criteria has been completed and verified. For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated.

6.3 Treatment Interventions

All patients enrolled in this trial will undergo surgical CABG. For each patient, two SVG vessels will be assigned to either a VEST-supported or a non-VEST-supported (control) therapy.

All procedures will be performed using a median sternotomy incision, cardiopulmonary bypass support, and cardioplegic arrest. The management of cardiopulmonary bypass and myocardial protection will be at the discretion of the surgeon, using standard techniques.

Coronary Artery Bypass Grafting (CABG)
For the vessel(s) assigned to control, coronary artery bypass grafting will be performed using standard surgical techniques. Conduit selection and harvesting methods will not be prescribed, except that an IMA will be utilized when an LAD graft is indicated. The technical details of bypass grafting will not be prescribed. Complete revascularization will be performed, within the judgment of the surgical investigator.

Surgical Procedure
Initial surgical intervention
The initial surgical procedure (CABG) must be reported on the surgical procedure form within 48 hours of the event. Operative data such as cross-clamp time, additional procedures performed at the time of the operation, and intra-operative blood transfusions, will also be collected. Data should be collected including but not limited to: procedure details (all grafts performed, venous, arterial, target arteries, graft diameters and lengths, vein harvesting and preservation technique, origin above/below the knee, varicosity), VEST implantation procedure (graft length and diameter assessment, model selection, serial number, technical success), randomization (time of all distal anastomoses completion, time of randomization, VEST supported graft, control graft).

6.3.1. Post-operative Medical Management
All patients will be prescribed statins and aspirin per practice guidelines (5) for 12 months. All other routine follow up will be performed in addition to study specifics detailed below.

6.4 Post-Randomization Data Collection

Study Visits
- Peri-operative
- Six weeks post-intervention *(± 2 weeks)*
- Six months post-intervention *(± 30 days)*
- 12 months post-intervention *(± 30days)* preceded by a phone call 6 weeks in advance
- Two, three, four, and five years post-intervention *(± 90 days)*

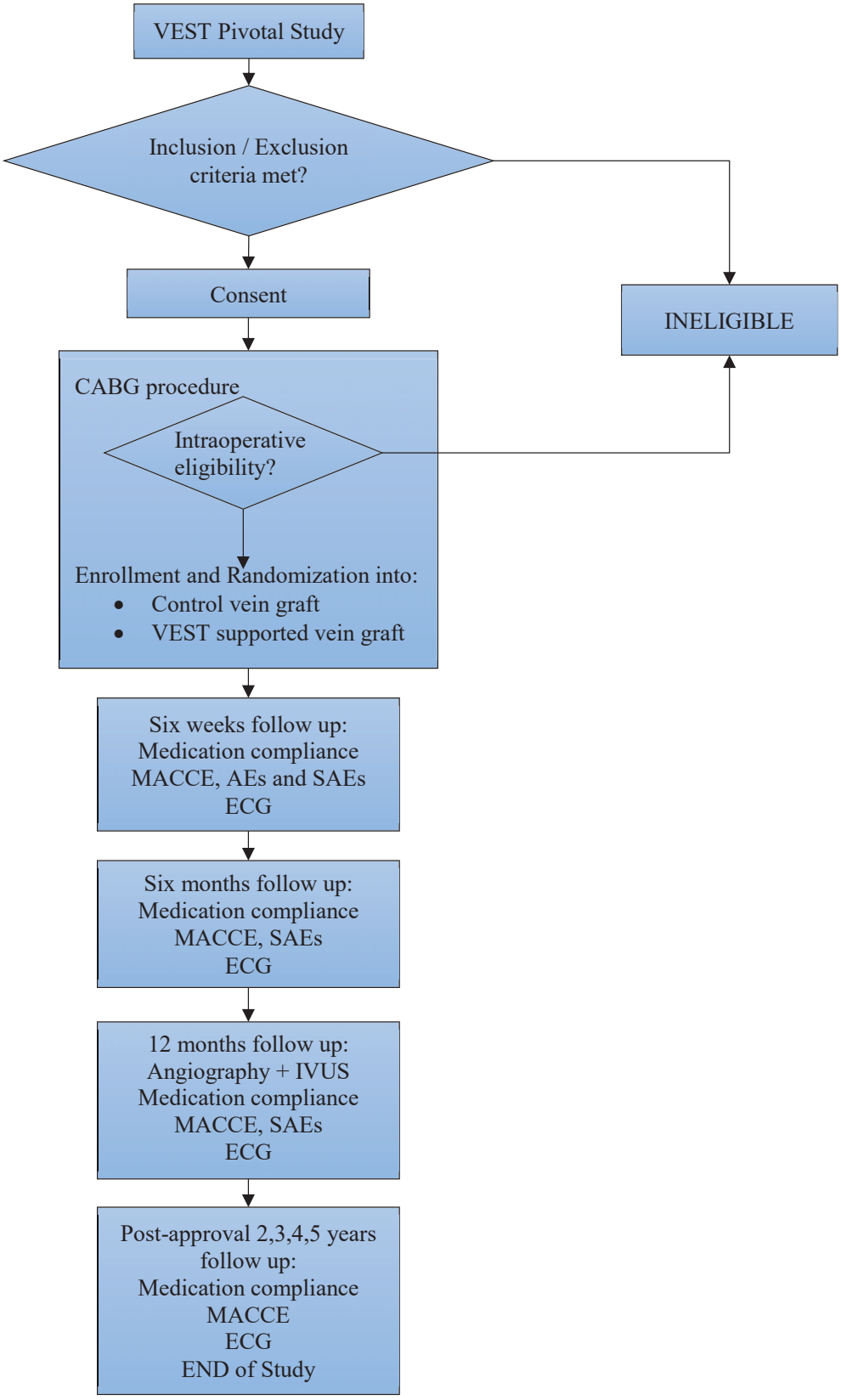

Figure 6: Study flow diagram

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

Medications
At 6 weeks (± 2 weeks), 6 months (± 30 days), 12 months (±30 days) and 2, 3, 4, 5 years (±90 days) post procedure and event-driven
All patients will be prescribed statins and aspirin per practice guidelines [5] for 12 months. These and all cardiovascular medications will be recorded at each study visit and also as indicated at the time of associated adverse events.

12 Lead ECG
At 6 weeks (± 2 weeks), 6 months (± 30 days), 12 months (±30 days) and 2, 3, 4, 5 years (±90 days) post procedure and event-driven
ECG results and interpretation will be collected.

Physical Examination
At 12 months (±30 days)
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Coronary angiography
At 12 months (±30 days)
Since this follow-up visit generates the primary endpoint data and completeness of data, each subject will be telephoned 6 weeks before the 1 year post-op date, to be reminded of the upcoming follow up visit and to schedule the appointment.

Coronary angiography – Contrast angiography will be attempted for all grafts and native vessels. Assessment of the patency/stenosis of the vein grafts and treated coronary arteries will be captured. Quantitative

Coronary Angiography (QCA) by a core lab will be used to analyze data from patent grafts. Data will include Fitzgibbon classification I, II, III), percentage of vessel stenosis, ectatic lesions, blood flow, blood velocity, lumen diameters averaged over 1 mm intervals, TIMI flow grade, Syntax Score of native coronary vessels only.

Intravascular ultrasound (IVUS)
At 12 months (±30 days)
The IVUS catheter will be advanced all the way through each of two study vein grafts (providing patency has been demonstrated by contrast angiography) and pulled back (motorized) at a constant rate.
Images will be recorded and uploaded via the EDC for offline analysis by the independent IVUS core lab.

Event Driven Data Collection
Serious Adverse Events
Event Driven
Detailed information regarding adverse events will be recorded at the time an adverse event becomes known. Relevant source documents and data will be collected including cost data pertaining to MACCE events. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All serious adverse events will be recorded until the patient completes 12 months follow up. MACCE will be collected throughout 60 months post randomization.

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

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

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

Neurologic Dysfunction Assessment
Event Driven
The Modified Rankin Scale (Appendix I) and NIHSS (Appendix II) should be administered by a certified evaluator at the time of a cerebrovascular thromboembolic event (within 72 hours following the event) and at the termination of trial follow-up to document the presence and severity of neurological deficits.

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

Additional Procedures
Event driven
All procedures following the initial study defined surgical intervention must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the operation is to address a complication, the coordinator must also complete an adverse event report.

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

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

Patients reserve the right to withdraw from the study at any time without jeopardy to future medical care. All follow-up assessments and procedures should be performed at the final study visit. They may also be administratively withdrawn if they do not return for follow-up visits. If an AE is ongoing at the time of the withdrawal, the treating investigator will attempt to follow the patient until the AE has resolved or stabilized or until follow-up is no longer possible.

If the patient misses a scheduled study visit, the site will attempt to contact the patient to determine and document the reason the patient has failed to return, to obtain any information on medication, adverse events, and to encourage compliance with the study visit schedule.

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

6.5 End Of Trial

The end of the pivotal trial will be declared when the last patient recruited completes the "12 months" visit. After study completion, patients will be followed by their respective doctors as per standard of care for patients in their condition. Follow-up will continue in the post-approval phase until the last patient reaches 5 year follow-up, as noted above.

6.5.1. Compliance with Protocol

The site Principal Investigator is considered responsible for compliance with the protocol at the investigational site. The Principal Investigator is also responsible for reporting all protocol deviations to the respective IRB and to the DCC. A representative of the DCC will make frequent contact with the Principal Investigator and his/her research staff and will conduct regular monitoring visits at the site to review patient data and device accountability records for compliance with the protocol, e.g., patient eligibility criteria, randomization assignments, device model selection, procedures performed, and follow-up visit schedule.

7. Risk-Benefit Considerations

In all clinical use to date (over 500 patients) the VEST has not been associated with any device related adverse events. The potential benefits of the VEST are in mitigation of vein graft disease parameters such as intimal hyperplasia, lumen non-uniformity and disturbed flow patterns. This potential effect has been observed over a follow up duration of 1 year in a 30 patient pilot study performed in the UK.
The VEST should be implanted by trained professional cardiac surgeons. Care should be taken to use the VEST according to the IFU. The VEST model should be carefully selected according to instructions for use. There is some risk of VEST interfering with side branch ligations or masking kinks in the vein graft, however this can be mitigated with training and careful attention to instructions. Once deployed and expanded on the vein graft, the VEST can, at any time, be recompressed, for inspection and correction of the vein graft, and subsequently re-expanded.

Potentially, if incorrectly placed, the VEST can lead to vein graft failure which in turn can lead to MI or need for additional intervention. This risk can be significantly mitigated by careful model selection, avoidance of metal clips, avoidance of interference with the anastomoses, and careful compliance with the IFU.
Additional potential adverse effects associated with the VEST may include the complications reported for conventional coronary artery bypass grafting procedure such as: vein graft failure, MI, stroke, ventricular fibrillation, impaired cardiac rhythm, infection, bleeding, death, or need for repeat revascularization.
In summary, while the potential benefits in mitigating vein graft disease are promising, the risks are mainly due to those associated with any CABG surgery and the adjunct use of the VEST ads minimal risk which can be mitigated with careful training and compliance with IFU.

Other risks associated with coronary artery disease and/or major surgery, such as CABG, apply to these patients, but are not expected to be influenced by use of the VEST.

8. Statistical Considerations

8.1 General Design Issues

This study is a prospective, multi-center, randomized clinical trial that will enroll patients with multi-vessel disease undergoing CABG. The novel VEST treatment will be randomly assigned with equal probability to either a right or left vein graft within each patient. For treatments assigned to left vein grafts, one will be randomly selected to serve as the "study graft". The nature of the treatments precludes masking of treating clinicians to treatment assignment; however, investigators will be masked to data from other clinical sites with the exception of serious, unexpected AEs, which must be revealed for IRB-reporting purposes. The trial's primary aim is to determine whether the VEST device is safe and effective for its intended use in supporting saphenous vein grafts used as conduits in patients who undergo CABG for coronary arteriosclerotic disease.

The within-patient design takes advantage of the positive correlation between intimal hyperplasia (IH) measured on grafts within the same patient, to produce a less variable measure of treatment difference, and so increase power compared to between-patient designs.

8.2 Analysis Sets

8.2.1. Safety Analysis Set

The safety analysis set will consist of all patients who are considered enrolled in the study, once they are randomized and an identification code is generated.

Handling of missing data: Only observed values will be used to analyze safety data; i.e. missing safety data will not be imputed.

8.2.2. Full Analysis Set

The full analysis set (FAS) will, consistent with ICH Guideline E9 (35), include all randomized vessels for whom the study procedure was initiated in either arm according to the intent-to-treat (ITT) principle.

8.3 Sample Size Justification

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing CABG. The primary endpoint of the study will be the intimal hyperplasia (plaque + media) area [mm^2] as assessed by IVUS at 12 months post randomization. Sample size is based on the assumption that IH will be normally distributed with standard deviation of 1.7 mm^2 in both the VEST supported and the unsupported vessels. We also assume that the mean IH in the unsupported vessel is 5.1 mm^2 and that the correlation between IH measured on grafts within the same patient is equal to 0.5. In addition, we anticipate that approximately 13% of patients will have the supported and/or unsupported grafts occluded or severely stenosed and so unable to have IH measured through IVUS; in approximately 50% of these patients IH will not be obtained in either graft, while in the rest, the occlusion will only affect one of the two graft, in 25% the VEST graft will be occluded and in 25% the control graft will be occluded). Although it is unclear to what extent occlusion is related to IH one year post CABG, we will treat missing values of IH resulting from occluded vessels as non-ignorable missing (see below section) using an imputation model that will penalize these vessels and will reduce the effect size. Therefore, we assume a conservative effect size of 0.4 mm^2, or a reduction of IH in the VEST vessels compared to the control vessel of about 8%.

Under these assumptions, fixing the power at 90% we need to enroll 190 patients, before adjustment for loss to follow-up.

Lost to follow up and refusals: The term "lost to follow-up" is used to describe an individual who has withdrawn consent to be in the study or who can no longer be located or assessed. Such individuals represent those for whom primary outcome assessment is no longer possible. We anticipate that the loss to follow-up rate or refusal to perform an IVUS in this study will be around 15%. To account for this loss to follow up rate a total of 224 eligible participants will be enrolled in the study.

8.4 Randomization Design and Procedure

Randomization will be performed only after the procedure has reached the stage where all distal anastomoses of venous grafts have been constructed. Subjects will be block randomized using a two-stage procedure:
Stage 1: Randomly assign to treatment either right or left grafts
Stage 2:

- If in Stage 1 the right vein graft was assigned to treatment, Stage 2 will assign randomly to Control one left vein graft (if there is only one left vein graft, it will be assigned to Control)
- If in Stage 1 the left side was chosen Stage 2 will assign randomly to Treatment one left vein graft (if there is only one left vein graft, it will be assigned to Treatment)

Only grafts originating proximally from the aorta will be considered for randomization. Sequential grafts will not be included in the study. In the left territory, where more than one graft may be performed, the vein grafts will be uniquely distinguished by their pre-measured length as "Longest Left" and "Shortest Left".

8.5 Statistical Analysis

8.5.1. Overview

Data will be summarized in tables using descriptive statistics (mean, standard deviation, median, minimum, maximum and number of subjects) for continuous data, or in frequency tables for categorical data. Tables will be presented by study arm and overall. Data listing by subject will be provided.

8.5.2. Subject Disposition

Subject disposition will be tabulated; the number of enrolled, exposed, prematurely terminated and completed subjects will be summarized, including the number of subjects in each analysis population.
A list of dropouts will be prepared including reason for discontinuation, and time of discontinuation.

8.6 Analysis of the primary endpoint

The primary outcome is the degree of intimal hyperplasia at 12 months post-surgical intervention, assessed by IVUS. The null hypothesis is that there is no difference in the 12-month intimal hyperplasia between vessels randomized to the VEST compared to control vessels. The primary null hypothesis will be tested in an intent-to-treat analysis using a two-tailed 0.05 alpha level. The analysis will be conducted using a Wilcoxon signed-rank test. A multiple imputation approach will be used to impute the intimal hyperplasia values of the occluded vessels as described below. In addition, we will also account for the occluded vessels in the computation of the Wilcoxon sign-rank test as follows. If two vessels in the same individual are both occluded, we will assign an absolute value of zero for the difference between the two scores irrespective of the imputed values. Pairs with a value of zero will be excluded from the computation of the test statistic as usual for the Wilcoxon rank-sign test. If only one of the two vessels is occluded in the same individual, then we will assign an absolute value equal to the difference between the observed and the imputed score. The sign associated with the rank for this difference, however, will be in favor of the non-occluded vessel. If both vessels are not occluded they will be treated as usual in the computation of the Wilcoxon sign-rank test.

We anticipate that roughly 13% of vessels will be obstructed and unsuitable for IVUS, and thus intimal hyperplasia will be measured only on non-obstructed vessels. Although the degree of intimal hyperplasia may be independent of the mechanism of obstruction, we will consider an obstructed vessel as a failed vessel in the analysis. Specifically, we will assume a non-ignorable mechanism (not missing at random or NMAR) for the data missing due to obstructed vessels.

We will address the problem of missing IVUS data by multiple imputation — i.e., creating several potential imputed observations for each missing data using a predictive modeling (36). The underlying model will use the pattern-mixture approach, which posits a separate distribution of the true IVUS measurement for missing and non-missing observations. The model will include the following subject specific covariates: hypertension, diabetes, hyperlipidemia, and smoking status; and the following vessel specific covariates: treatment assignment, coronary territory, vein harvest and preservation techniques.

Let Y represent the continuous outcome variable (i.e. intimal hyperplasia) and let R be an indicator variable that assumes different values according to whether Y is observed or missing. Under a pattern-mixture model, the joint distribution of the outcome Y and the missing indicator variable R, $f(Y,R)$, is factorized into the density of the outcome, conditional on the pattern of missingness of Y, $f(Y|R)$, and the marginal distribution of the missing indicator variable, $P(R)$.

$$f(Y,R)=f(Y|R)P(R)$$

In longitudinal studies, the probability distribution $P(R)$ refers to the probabilities of the different possible patterns of missingness. In this situation we distinguish only two patterns of missing data: we define a case to be complete $(R=1)$ if a vessel is able to be evaluated at follow-up, and to be incomplete $(R=0)$ if the follow-up measurement is missing due to occlusion.

Under the NMAR framework, the density $f(Y|R)$ is specified differently depending on whether $R=0$ (Y is missing) or $R=1$ (Y is observed), reflecting the fact that the missing values may come from a different distribution than the observed ones. In this study, we will assume that the distribution function of intimal hyperplasia is normal, with $f(Y|R=1)\sim N(\mu, \sigma^2)$ for the observed data and $f(Y|R=0)\sim N(\mu+\delta, \gamma\sigma^2)$ for the missing data. The parameters δ and γ are sensitivity parameters. In order to "penalize" the obstructed vessels we will assume that δ is positive to reflect, on average, larger values of intimal hyperplasia. Specifically, we will assume that the non-observed values come from a normal distribution with mean equal to the 90th percentile of the distribution of intimal hyperplasia in the VEST I trial, which was equal to 6.84 mm^2.

The procedure will be implemented in two stages: First we will create of a set of imputations for intimal hyperplasia for each patient with missing data due to an occluded vessel. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. Characteristics of the vessels, like laterality and length as well as patients' characteristics will be used to inform the predictive models. This corresponds to the usual imputation under a missing at random (MAR) mechanism. In the second stage, values will be generated from a prior distribution $N(\delta, \sigma_\delta^2)$, where δ is such that $\delta+\mu$ is equal to the 6.84 mm^2, and added to the imputed response from the first stage.

We will repeat the imputation process 30 times to achieve maximal stability of the procedure. Following Rubin, we will conduct a separate analysis for each completed dataset using a Wilcoxon signed-rank test as described above. Li et al (37) method of combining the significance levels from the 30 analyses will be used to test the mean difference between the intimal hyperplasia of the treated and control vessels.

For simplicity our primary analysis will not be stratified by clinical center, although the randomization will stratify by clinical center. This should result in only a small loss of efficiency.

Sensitivity Analysis
We will conduct a series of sensitivity analyses to determine the stability of the estimate of the treatment effect obtained with the multiple imputation pattern-mixture approach. Specifically, we will work with different values of the sensitivity parameter δ and γ to determine how our assumptions about the distribution of the missing data influence the results. For example, assuming $\delta = 0$ corresponds to a missing-at-random (MAR) assumption, which posits that there is no information in the fact that a vessel is occluded and therefore cannot be measured. These analyses will allow us to determine how large δ has to be to change the outcome of the final analysis with respect to statistical significance of the treatment effect.

Crossovers
Vessels randomized to VEST but not supported will be considered crossovers. Similarly, vessels randomized as control but VEST supported will be considered cross-overs. We anticipate very few cross-overs in this trial. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect of on trial outcomes.

Missing Data due to Missed Visits
Patients will be scheduled for a 12-month IVUS study, and patients should be carefully screened prior to randomization regarding their willingness to undergo an IVUS study. Despite this screening and ongoing communication with patients regarding the importance of study endpoint assessment, we anticipate that there will be 10-15% missing primary endpoint assessments. Patients missing primary endpoint assessments due to loss to follow-up are accounted for in the sample size calculation.

8.7 Analysis of Secondary Confirmatory Endpoints

Following are the study's two secondary confirmatory hypotheses that will be tested in FAS in the order presented using a sequential strategy:
Secondary Confirmatory I

H_0: (Lumen Diameter Uniformity)$_{VEST}$ = (Lumen Diameter Uniformity)$_{SOC}$

H_1: (Lumen Diameter Uniformity)$_{VEST}$ ≠ (Lumen Diameter Uniformity)$_{SOC}$

Where lumen diameter is measured using Fitzgibbon classification (scale of 1 to 3) as described in Section 5.2.
Hypotheses will be tested using the Wilcoxon Sign-rank test with two-sided Alpha = 0.05. We will declare success on this endpoint if we will have succeeded on the primary efficacy endpoint and rejected the null hypothesis in this section as a result of mean rank for VEST being lower than SOC.
[that is: (Lumen Diameter Uniformity)VEST > (Lumen Diameter Uniformity)SOC].

Secondary Confirmatory II

H_0: (Graft Failure)$_{VEST}$ = (Graft Failure)$_{SOC}$

H_1: (Graft Failure)$_{VEST}$ ≠ (Graft Failure)$_{SOC}$

Where graft failure ("yes" or "no") is determined as described in Section 5.2.
Hypotheses will be tested using McNemar's test for paired binary observations with two-sided alpha = 0.05. We will declare success on this endpoint if we will have succeeded on both confirmatory endpoints. [that is: (Lumen Diameter Uniformity)VEST > (Lumen Diameter Uniformity)SOC AND (Graft Failure)VEST <(Graft Failure)SOC].

8.8 Analysis of Additional Secondary Endpoints

The following additional secondary endpoints will be analyzed:

Intimal hyperplasia: (plaque + media) thickness [mm] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (supported and unsupported) and is measured as a continuous variable. This secondary endpoint will be analyzed using mixed models with patients as random effects.

TIMI flow grade assessed by angiography at 12 months on the following 4-point ordinal scale:

- Grade 0 – No perfusion
- Grade 1 – Penetration without perfusion
- Grade 2 – Partial perfusion
- Grade 3 – Complete perfusion

This secondary endpoint will be analyzed using a Wilcoxon signed-rank test.

Graft failure at 12 months, as defined above, separately for right and left territories. This endpoint will be analyzed using McNemar's test for binary observations.

Repeat revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) over the 5 years of observation. This endpoint will be analyzed using McNemar's Test for paired 2 x 2 tables.

Lumen diameter uniformity expressed by the coefficient of variance (CV) by QCA at 12 months, computed for each graft separately and scored continuously as follows:
$CV_{Uniformity} = SD_{Diameter}/Mean_{Diameter}$

Ratio of vein graft lumen diameter to target artery lumen diameter by QCA at 12 months.
The latter two endpoints will be analyzed using mixed-effect models with patient as random intercept.

8.9 Clinical Events

The clinical events will be tabulated and characterized using descriptive statistics. Time to death will be described using a Kaplan-Meier curves, adverse events (including MACCE) will be described as rates and proportions. 95% confidence intervals will be constructed around the point estimates.

8.10 Interim Analysis

There is no planned interim analysis.

8.11 Five-year Follow-up

Patients participating in this trial will be followed for an additional 4 years after completing the 12-month pivotal trial to assess the following endpoints:

- Revascularization rate for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years.
- Rate of MI culprit vessels, for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years.
- Time to revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery).
- Time to MI in culprit vessels, for supported and unsupported vein grafts (or respective bypassed target coronary artery).

Rates at 3 and 5 years will be analyzed by Fisher's exact test. Time-to-event endpoints will be described using Kaplan-Meier curves and analyzed using the Cox Proportional hazards model—with and without adjustment for individual covariates. While these analyses are pre-specified in the protocol, this study is not powered for these endpoints.

9. Data Collection, Study Monitoring, and Data Disclosure

9.1 Data Management

All study data will be entered in the web-based electronic data capture (EDC) system (specified in detail in the Operations Manual). Study personnel requiring access will have their own Login/Password. Access to

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

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

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data and/or values that are outside the range of what is typically considered to be physiologically possible). Monitors will enter these queries through the EDC system for site coordinators to either correct or verify.

9.2 Study Monitoring and Source Data Verification

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

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

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

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

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

The monitor will verify a minimum of the following variables for all patients: signed informed consent, eligibility criteria, date of enrollment, adverse events, and mortality. These data will be 100% source data

verified. All other data collection will be monitored as indicated by the data completeness and accuracy at each clinical site.

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

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

10. Organization of the Study

This section describes the overall study organization. The study is conducted in the clinical centers who participate in the Cardiothoracic Surgical Trials Network (CTSN). The trial is sponsored by VGS. The following committees and institutions will be involved in the administration of the study.

10.1 Event Adjudication Committee (EAC)

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all serious adverse events and causes of mortality. The individuals who will serve on the committee have no formal involvement or conflict of interest with the clinical trial or the DCC, and will be appointed by the DCC. The committee will consist, at least, of a cardiothoracic surgeon, a cardiologist, and a neurologist. The EAC will meet 8 times annually or as needed to review outcomes data for each subject enrolled.

10.2 Data and Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians, biostatisticians, ethicists, neurologists and bioengineers who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC, or the clinical sites. The DSMB will act in a senior advisory capacity to the DCC and VGS regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events and mortality. They will communicate their findings directly with the DCC. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

10.3 Clinical and Data Coordinating Center (DCC)

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

10.4 IVUS/Coronary Angiography Core Lab

The Coronary Angiography Core Lab, located (TBD), is directed by (TBD). All angiograms and intravascular ultrasounds will be performed according to a standardized protocol (see Manual of Operations) and will be centrally analyzed.

10.5 Site Qualification

The study will be conducted in up to 20 clinical centers participating in the Cardiothoracic Surgical Trials Network (CTSN). Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the Data Coordinating Center and Sponsor with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile
The following information will be collected for all surgeons, cardiologists, coordinators and other investigators who participate in the study: contact information including address, telephone, fax, and email. The surgeon, cardiologist, surgical physicians' assistant or nurse practitioner and coordinator must provide their CVs, Conflict of Interest Statement and Financial Disclosure Certifications, and Institutional Health Insurance Portability and Accountability Act (HIPAA) and Human Subjects Protection Certificates to the DCC prior to initiation of enrollment.

Qualifications and Training
Clinical investigators will be cardiothoracic surgeons with expertise in CABG. To qualify as a surgeon participating in this trial, the surgical investigator must have performed at least 20 on pump CABG procedures annually averaged over two years as an attending surgeon.

Cardiology investigators will have expertise in diagnostic angiography and IVUS and must have performed at least 10 procedures annually averaged over two years as an attending cardiologist.

Surgical physicians' assistants (PA) or nurse practitioners (NP) must have performed at least 20 vein graft harvest procedures annually averaged over two years since licensure.

Surgeon and cardiologist training for VEST
The surgical investigator, PA and/or NP will receive onsite training from the VGS representative. All cardiology investigators will receive an acquisition protocol for the angiography and IVUS.
All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

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

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

Site Approval
The following documents must be collected prior to site approval and opening to patient enrollment:

- FDA IDE approval
- Signed Clinical Study Agreement with Vascular Graft Solutions, Ltd.
- Signed investigator agreement as approved in IDE G150225
- Signed Conflict of Interest Statements
- Completed Delegation of Authority Log
- Signed and dated CVs for all staff on Delegation of Authority Log
- Privacy training (HIPAA) and Human Subjects training documentation (as required by local institutional guidelines) for all staff on Delegation of Authority Log
- Current licenses for all staff on Delegation of Authority Log
- NIH Stroke Scale and Modified Rankin Scale Training Certification for delegated staff
- IRB roster
- IRB approval for protocol, informed consent document, HIPAA authorization
- Clinical Center Laboratory Certification

- Laboratory Normal Ranges
- Surgical Certification forms for Surgeons
- Cardiology Certification for Cardiologist
- NP/PA Certification forms
- Surgeon, NP/PA VEST training documents
- Signed Document Approval Form for protocol
- Study-specific training documents

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

10.6 Patient Confidentiality

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

10.7 Publications

The Sponsor and CTSN investigators plan to publish the outcomes of this study. Publication in writing and/or orally will take place after completion of the 1 year data collection and analysis or sooner if the study is terminated. Publication arrangements are detailed in the CTA.

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12. APPENDIX I: MODIFIED RANKIN SCALE (MRS)

Instructions: Assessment should be completed by a certified evaluator.

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

☐	0=	No symptoms at all
☐	1=	No significant disability, despite symptoms; able to carry out all usual duties and activities
☐	2=	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
☐	3=	Moderate disability; requiring some help, but able to walk without assistance
☐	4=	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
☐	5=	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

13. APPENDIX II: NIH STROKE SCALE (NIHSS)

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

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

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

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

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

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

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

1c. LOC Commands
Say to the patient "open your eyes...now close your eyes" and then "Make a fist...now open your hand". Use the non-paretic limb. If amputation or other physical impediment prevents the response, use another suitable one step command. The priming phrase is not scored, and these are used only to set the eyes or hand in a testable position. That is, the patient may be asked first to open the eyes if they are closed when you begin the test. Scoring is done on the second phrase "close your eyes". Count the number of incorrect responses and give credit if an unequivocal attempt is made to perform the operative task, but is not completed due to weakness, pain or other obstruction. Only the first attempt is scored and the questions should be asked only once.

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

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

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

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

6. Motor Arm-Left
See explanation of 5.

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

8. Motor Leg-Left
See explanation of 7.

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

Please indicate presence of ataxia in arms and legs.

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

11. Best Language

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

12. Dysarthria

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

13. Extinction and Inattention (formerly Neglect)

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

Total Score: Please provide the total score for the subject as determined by the 11 categories of questions. Do not include scores of "9" in total.

Vascular Graft Solutions Ltd.

Protocol number	CD0131
Study title	A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support
Sponsor	Vascular Graft Solutions Inc. c/o Broadview Ventures 265 Franklin Street, Suite 1902 Boston, MA 02110 Phone: 617.341.8121
VEST Manufacturer	Vascular Graft Solutions Ltd. (VGS) 24 Raoul Wallenberg St. Tel Aviv, Israel 6971921 Tel: +972-3-5499054 Fax: +972-3-6024966
Sponsor Contact	Orit Yarden, PhD Mobile: +972-54-3073050 orit@graftsolutions.com
Clinical and Data Coordinating Center (DCC)	International Center for Health Outcomes and Innovation Research (InCHOIR) Coordinating Center for the Cardiothoracic Surgical Trials Network (CTSN) Icahn School of Medicine at Mount Sinai New York

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Sponsor in confidence and.

I have read this protocol in its entirety and I agree to all aspects.

Investigator printed name	Site
Signature	Date

RETURN TO SPONSOR WITH THE ATTACHED PROTOCOL

CONTENTS

Definitions, Acronyms & Abbreviations

21CFR	Code of Federal Regulation number 21
AE	Adverse event
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CFR	Coronary Flow reserve
CK-MB	Creatine Kinase-Muscle/Brain
CV	Coefficient variance
CT	Computed tomography
CTSN	Cardiothoracic Surgical Trials Network
Cr	Creatinine
CRF	Case report form
cTn	Cardiac troponin
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
FDA	Food and Drug Administration
FFR	Fractional Flow reserve
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IABP	Intra-aortic balloon pump
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IFU	Instructions for use
IRB	Institutional Review Board
IVUS	Intra vascular ultrasound
LAD	Left anterior descending coronary artery
LBBB	Left bundle branch block
LIMA	Left internal mammary artery
LOS	Length of stay
iMA	Internal mammary artery
MACCE	Major adverse cardiac and cerebrovascular events
MI	Myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NP	Nurse Practitioner
NYHA	New York Heart Association
PA	Physician's Assistant
PCI	Percutaneous coronary intervention
PI	Pulsatility index
PMA	Premarket approval
PTT	Partial Thromboplastin Time
SAE	Serious adverse event
SMC	Smooth muscle cell
SOC	Standard of care
SOP	Standard operating procedure
SVG	Saphenous vein graft
QCA	Quantitative coronary angiography
TIMI	Thrombolysis in myocardial infarction
TTFM	Transit time flow measurement UADE Unanticipated adverse device effect
URL	Upper reference limit
VEST	Venous external support
VGS	Vascular Graft Solutions Ltd.

Synopsis

STUDY TITLE	A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support
STUDY	VEST™ Venous External Support
TREATMENT PHASE	Pivotal study under an Investigational Device Exemption (IDE) Primary endpoints at 12 months will be used to support a PMA application. Long term data, up to 5 years follow-up, will be monitored in the post-approval period.
CLINICAL SIGNIFICANCE	Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease. Despite the proposed benefits of multiple arterial grafts, autologous saphenous vein grafts (SVGs) are still the most frequently used bypass conduits in CABG. Progressive SVG failure after CABG remains a key limitation to the long-term success of surgery.
OBJECTIVES	To demonstrate the safety and effectiveness of the VEST for its intended use: Limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease.
STUDY DESIGN	Prospective, multi-center, randomized, within-subject-controlled , trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison between two sets of SVGs: A VEST supported set; and an unsupported set.
ENDPOINTS	Primary endpoint: Intimal hyperplasia (plaque+media) area [mm^2] as assessed by IVUS at 12 months. Occluded vessels are accounted for in the analysis of the primary endpoint. Secondary confirmatory endpoints: 1. Lumen diameter uniformity, assessed by angiography for each graft separately and expressed by the Fitzgibbon classification (22), on a 3-point ordinal scale: I – No intimal irregularity II – Irregularity of <50% of estimated intimal surface III – Irregularity of >50% of estimated intimal surface 2. Graft Failure (≥50% stenosis) by cardiac angiography at 12 months Clinical Events 1. Serious adverse events 2. MACCE 3. Mortality 4. Hospitalization
RX ARMS	In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Patients will be block randomized by territory and/or by SVG length. If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will randomly assign the treatment and control vessels by their lengths.

COHORT	Sample size 224 subjects will be enrolled in this trial. Inclusion criteria 1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation. 2. Age 21 years or older. 3. Planned and scheduled on-pump CABG. 4. Two or more vein grafts to native vessels having at least 75% stenosis and comparable runoff. 5. IMA graft indicated for the LAD. Additional arterial grafts may be considered based on practice guidelines. 6. Appropriately sized and accessible target coronary arteries, with a minimum diameter of 1.5 mm and adequate vascular bed (without significant distal stenosis), as assessed by pre-operative cardiac angiography and verified by diameter gauging intraoperatively. Exclusion criteria 1. Concomitant non-CABG cardiac surgical procedure. 2. Prior cardiac surgery. 3. Emergency CABG surgery. 4. Contraindication for on-pump CABG with cardioplegic arrest (e.g., severely calcified aorta). 5. Calcification at the intended anastomotic sites, as assessed upon opening of the chest and before randomization. 6. Severe vein varicosity as assessed after vein harvesting and before randomization. 7. History of clinical stroke within 3 months prior to randomization. 8. Severe renal dysfunction (Cr>2.0 mg/dL). 9. Documented or suspected untreated diffuse peripheral vascular disease such as: carotid stenosis or claudication of the extremities. 10. Concomitant life-threatening disease likely to limit life expectancy to less than two years. 11. Inability to tolerate or comply with required guideline-based post-operative drug regimen (antiplatelet plus statin) and/or inability to take aspirin. 12. Inability to comply with required follow-ups including angiographic imaging methods (e.g. contrast allergy). 13. Concurrent participation in an interventional (drug or device) trial.
DATA AND SAFETY MONITORING	An independent Data and Safety Monitoring Board (DSMB) will oversee patient safety and overall progress of the study. An independent Event Adjudication Committee (EAC) will review and adjudicate adverse events occurring during this trial. Stopping guidelines for safety will be developed based upon trial data.
DURATION	Accrual is expected to take 12 months, and all patients will be followed for the primary endpoint at 1 year post-randomization, with annual visits until 5 years post-randomization

Data Collection Schedule

Assessment	Screening/ Baseline	Intra-Op	6 Weeks	6 Months	12 Months	Years 2,3,4,5
Visit Windows	w/in 30 days		+/- 2 weeks	+/- 30 days	+/- 30 days	+/- 90 days
General						
Informed Consent	X					
Release of Medical Information	X					
Screening Log and Registration	X					
Medical History	X					
Laboratory Assessment	X					
Medications	X		X	X	X	X
Physical Exam	X				X	
ECG	X		X	X	X	X
Phone call to subject					X (6 weeks prior to 1 year post-op date)	
Coronary Angiography[1]	X				X	
Eligibility Criteria	X					
Intravascular Ultrasound					X	
Randomization[2]		X				
Surgical Procedure		X				
TTFM data		X				
Event Driven Data						
Adverse Events		X	X			
Serious Adverse Events		X	X	X	X	
MACCE		X	X	X	X	X
Procedures		X	X	X	X	X
Hospitalization	X	X	X	X	X	X

[1] Angiography at screening must be within 6 months

[2] The randomization procedure will be performed inside the OR after confirmation by the surgical team of the patient's eligibility

1. Objectives

The purpose of this study is to demonstrate the safety and effectiveness of the VEST for its intended use: limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting (CABG) procedures as treatment for coronary arteriosclerotic disease.

This protocol describes a prospective, multi-center, randomized, within-subject-controlled, open label clinical trial to evaluate the safety and effectiveness of the VEST, an external mechanical support for autologous saphenous vein grafts that are created during Coronary Artery Bypass Surgery (CABG).

This study is designed to provide safety and effectiveness data with the primary endpoint measured over 12 month follow up post index CABG procedure. Patients will continue to be followed annually up to 5 years in the post-approval period.

2. Background and Rationale

2.1 The Clinical Need

Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease (1). Despite the proposed benefits of multiple arterial grafts (2), autologous saphenous vein grafts (SVGs) are still, numerically, the most frequently used bypass conduits in CABG. However, progressive SVG failure after CABG remains a key limitation to the long-term success of surgery (3, 4). As many as 25% of SVGs occlude within 1 year of CABG; an additional 1-2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which are disease free (5).

Intimal hyperplasia and subsequent SVG failure have significant effects on clinical outcomes such as onset of angina, need for revascularization intervention (surgical or percutaneous), myocardial infarction (MI), and death. The localized areas of "adaptive" intimal hyperplasia that occur in native human arteries have been defined by the American Heart Association Council on Arteriosclerosis as "atherosclerosis-prone regions" (6). FDA recognizes mitigation of intimal hyperplasia as the main effect mode of the drugs eluted by coronary stents (7). In a similar process the extensive intimal hyperplasia throughout the length of a vein graft may effectively create a diffuse atherosclerosis-prone region (4).

The pathophysiology of SVG failure is a well-documented consequence of several intrinsic and extrinsic factors (3, 4). Beyond short-term factors and technical surgical errors, stenosis and failure is dominated by proliferation of intimal hyperplasia which is the foundation for graft atheroma and subsequent vein graft failure, ultimately resulting in higher rates of coronary re-intervention (stenting or re-do CABG), stroke, MI and death in patients with failed SVGs.

Several factors contribute to SVG failure in the short term. Even under optimal conditions, saphenous vein harvesting results in endothelial cell loss, damage to medial smooth muscle cells (SMC), and disruption of micro-perfusion to the vessel wall (10).

Following implantation into a vigorous arterial circulation system, saphenous veins may experience abrupt hemodynamic changes with increased blood pressure, shear stress, wall tension, and pulsatile flow (11,12,13). Among these, high circumferential wall stress and low wall shear stress coupled with intraluminal irregularities are the dominant promoters of vein grafts stenosis (14,15).

Evidence from experimental studies has indicated a strong causal relationship between increased circumferential wall stress and activation of various intracellular signaling molecules (15). These chains of events stimulate vascular smooth muscle cells proliferation and migration in the media, accelerating the progression of intimal hyperplasia. From the standpoint of hemodynamic adaptation, the ratio of lumen radius to wall thickness in vein grafts tends to approach the same value as that in run-off arteries for maximum efficiency of blood transportation. Accordingly, structural remodeling of the venous lumen and wall occurs (13). An external vein graft support has the ability to limit abrupt dilatation and associated wall stretch, reinforce the venous wall thus absorbing pressure, and subsequently mitigate and suppress the proliferative reaction induced by high wall stress.

In addition to significant effects on the vein graft wall, the arterialization of the vein graft results in disturbed and turbulent flow patterns within the vein grafts. The irregular remodeling and dilatation result in a non-uniform lumen which in turn results in disturbed turbulent and oscillatory flow which in turn promote

atherogenesis (16). The geometric diameter mismatch between artery and vein also results in flow discrepancies (13,14). An external vein graft support such as the VEST is designed to regulate flow patterns by enhancing lumen uniformity.

Over the longer term, proliferation of intimal hyperplasia renders the vein graft lumen vulnerable to atherosclerosis leading to SVG stenosis and occlusion (17,18,19,20,21).

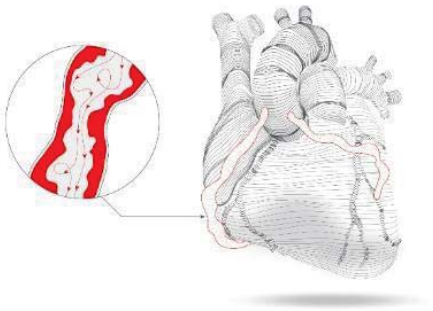

Figure 1: Vein graft remodeling flow disturbances

2.2 Perivascular External Support

Attempts to mitigate intimal hyperplasia and SVG failure have been the focus of intense clinical research. Pharmacological attempts, including Edifoligide (8) and aspirin + clopidogrel (9), have both failed to reduce SVG failure or mitigate intimal hyperplasia, respectively at 12-18, months after CABG.

Mechanical external supports for SVGs have shown considerable promise in pre-clinical testing with reduction of vessel dilatation and stretch, proliferative intimal hyperplasia and medial thickening (24, 25, 26, 27, 28). External support also reduces the diameter mismatch between the vein graft and the host coronary artery and increases the lumen uniformity (29). Furthermore, external stents have been shown to facilitate adventitial neovascularization that counteracts damage to the vein graft's vasa vasorum during harvesting (30, 31). However, limited clinical data has been published to date with such devices and adoption into clinical practice is lacking. In two randomized self-controlled studies of other devices intended to provide permanent support to SVGs, Murphy et al (32) describe 100% occlusion of supported SVGs at six months and Schoettler et al (33) report a 72% occlusion rate at nine months. Both these external stents (Figure 2) required gluing and/or suturing to the vein graft in order to optimize length and diameter match and to prevent migration, which may explain their lack of success.

The eSVS Mesh described in Schoettler et al (33) requires both application of fibrin glue and suturing the anastomoses through the device mesh. The anastomoses are probably the most sensitive part of the CABG procedure and are the most prone to technical errors. In addition, the application of fibrin glue on vein grafts has been tested in-vivo in a porcine model and has been histologically shown to induce an increase of graft thickening (34) and may contribute to vein graft failure (33). This is of course counterproductive to the attempts of external support devices to inhibit graft remodeling.

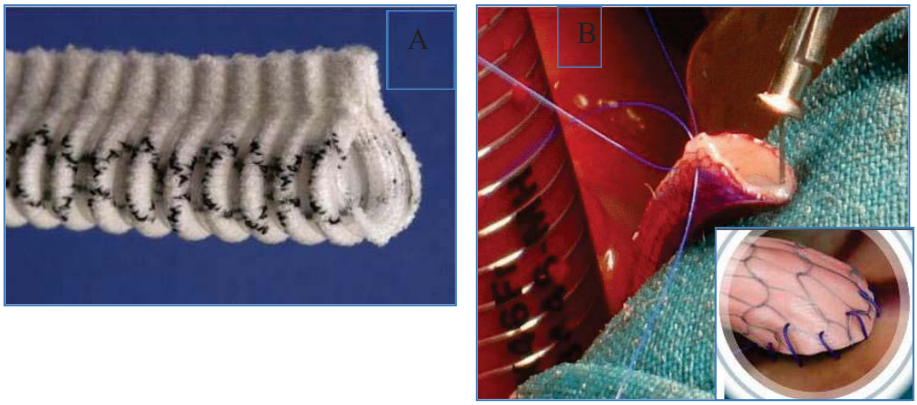

Figure 2: A: Extent external support (Schoettler et al); B: eSVS MEsh esternal support (Murphy et al)

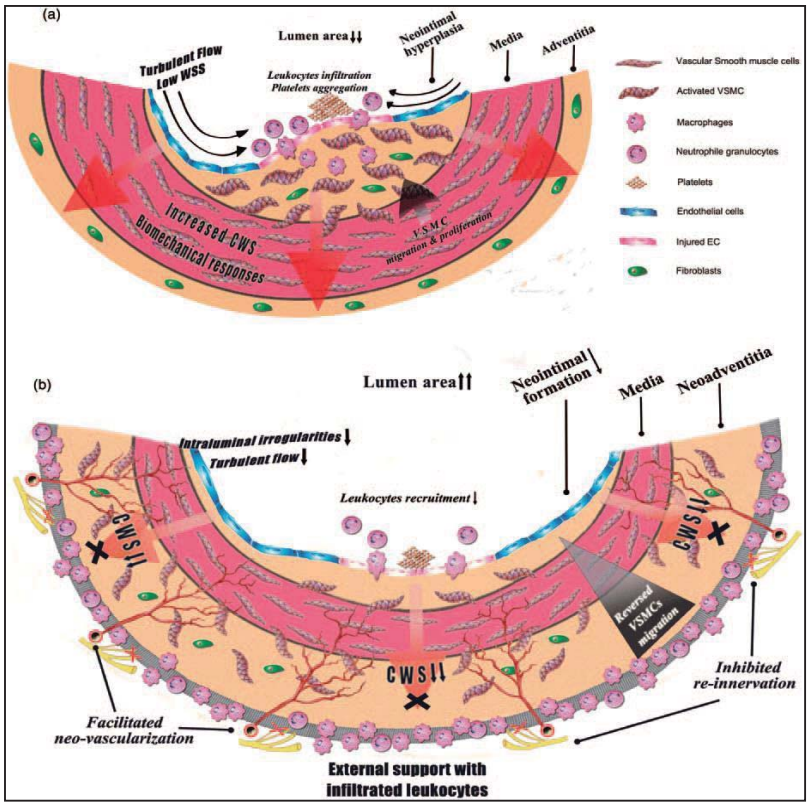

Figure 3: (Adapted from Hu & Wan (13)): Schematic diagram illustrating the pathogenesis of venous wall over-thickening and the mechanisms involved in external stenting of the vein graft: (a) failure of unsupported vein grafts due to neointimal hyperplasia and incorporated atherogenesis; (b) external prostheses preventing the venous wall from abrupt biomechanical changes through perivascular mechanical support, redirecting smooth muscle cell migration, facilitating neo-adventitial revascularization, and inhibiting re-innervation. CWS: circumferential wall stress; EC: endothelial cells; VSMC: vascular smooth muscle cells; WSS: wall shear stress

Table 1: Processes of intimal hyperplasia formation and the respective external support mechanisms of action

Intimal hyperplasia proliferation mode	External support potential inhibitory effect (13)
Wall stretch and activation of signaling molecules triggering proliferation and migration of smooth muscle cells.	An external support enables external reinforcement, limits abrupt dilatation and thus minimizes the wall stretch trigger
Remodeling of the vein graft directed at achieving arterial wall thickness to lumen radius ratio causes lumen irregularities.	An external support inhibits remodeling and promotes lumen uniformity
Turbulent and oscillatory flow caused by lumen irregularity adversely affects the blood-endothelial interface, activating smooth muscle cells and platelet aggregation.	An external support maintains lumen uniformity, hence inhibits turbulence and flow oscillations.
Dysfunction of vascular vasa-vasorum due to the harvesting procedure causes migration of smooth muscle cells and fibroblasts towards the inner layer, oxygenating by the oxygen rich arterial circulation.	An external support triggers growth of neo-adventitial vasculature which supplies the venous wall and inhibits inward migration of smooth muscle cells.
Inward migration of smooth muscle cells	An external support causes foreign body reaction which promotes outward redirection of the migration of smooth muscle cells and fibroblasts (accumulating around the external support) instead of migrating inwards.

2.3 The VEST

VEST (Venous External Support) manufactured by Vascular Graft Solutions Ltd, is an external mechanical support for autologous saphenous vein grafts that are created during Coronary Artery Bypass Surgery (CABG). The VEST (Figure 4, Figure 5) is deployed over the vein graft by the cardiac surgeon during the CABG procedure in a simple user-friendly manner. The implantation process takes only 1 minute and does not add any significant time to the overall CABG duration. The VEST does not require attachment to the vein graft or to the anastomoses by any external means (sutures or glue).

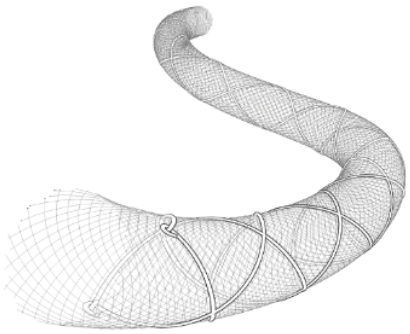

Figure 4: The VEST

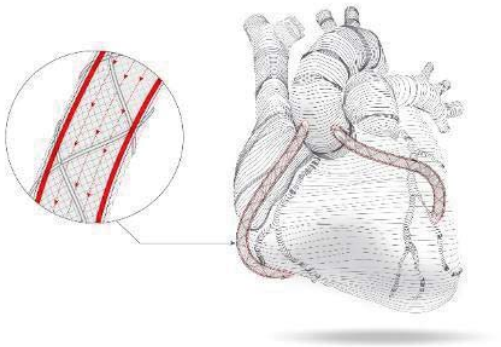

Figure 5: Two VESTs deployed over SVGs

The VEST is designed to target the underlying factors leading to SVG disease progression and, in particular, proliferation of intimal hyperplasia. Several effect modes are combined to deliver the desired effect:

- Prevention of post implantation dilatation
- Restraining wall tension
- Prevention of graft ectasia (segmental dilatation)
- Mitigation of occlusive thrombosis
- Enhancing diameter match with coronary artery
- Maintaining lumen uniformity
- Improving flow patterns

2.3.1. Intended Use

The VEST is indicated for use in limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease. Information on product design and accessories is available in the device Instructions for Use.

3. Overall Study Design

3.1 Structure

This is a prospective, multi-center, randomized, within-subject-controlled trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison of the primary endpoint between two sets of SVGs: A VEST-supported set; and a non-supported set. While the primary endpoint is assessed at 12 months post randomization, patient follow-up will continue for 5 years in order to demonstrate long-term outcomes of the VEST.

3.2 Rationale for Primary Endpoint

The primary endpoint is the degree of intimal hyperplasia at one year as assessed by IVUS. Missing IVUS data due to vessel occlusion will be imputed using a non-ignorable mechanism (not missing at random). The rationale for analyzing this endpoint in this manner is that it reflects efficacy in reducing intimal hyperplasia

and does not exclude occluded vessels, which are a safety concern. Proliferation of intimal hyperplasia is an ongoing process over years post CABG. The presumed efficacy of the VEST is its ability to slow down the rate of intimal hyperplasia formation. This study is designed to evaluate the difference between intimal hyperplasia area of VEST supported and unsupported vein grafts at one year after randomization. The within-subject design has advantages in that it reduces between-treatment variability by having each patient serve as their own control, but affects the ability to attribute serious adverse events to a treatment. We will capture serious adverse events in this trial, including MACCE.

3.3 Randomization

For every patient, a pair of grafts will be designated for participation in the trial; one to be supported with the VEST device and the other to serve as a control. Grafts to the LAD do not participate in the randomization.

Patients will be block randomized by territory and/or by SVG length.

If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will assign the treatment and control vessels by their lengths.

Only grafts originating proximally from the aorta will be considered for randomization. ***Sequential grafts will not be included in the study.*** Where more than one graft may be performed per territory, the vein grafts will be uniquely distinguished by their pre-measured length as "Longest" and "Shortest". This design will allow for within-subject comparisons, which is expected to increase power relative to a between-subject design.

To prevent any bias as well as exclude any ineligible patients, randomization will be performed only after the procedure has reached the stage where all venous bypass distal anastomoses have been constructed.

3.4 Masking

The nature of the study precludes masking surgeons from treatment assignment. In order to prevent selection bias, randomization into treatment assignment is performed intraoperatively only after all distal anastomoses have been completed (see section 6.2). Investigators will also be blinded to all data from other clinical sites, as well as the primary outcomes data and aggregate data regarding clinical outcome. Serious unexpected AEs will be reported to Institutional Review Board (IRB) as usual. Clinical events including serious and protocol-defined adverse events will be reviewed by an Event Adjudication Committee. All angiograms and intimal hyperplasia scoring will be analyzed, according to predefined analysis protocols, by independent core laboratory personnel who will be blinded to clinical outcomes.

4. Study Population

4.1 Number of Patients

A total of 224 subjects will be enrolled in up to 20 US and Canadian sites.

4.2 Eligibility Criteria

4.2.1. Inclusion Criteria

Eligible patients will meet all the following inclusion criteria:

1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation.
2. Age 21 years or older.
3. Planned and scheduled on-pump CABG.
4. Two or more vein grafts to native vessels having at least 75% stenosis and comparable runoff.
5. IMA graft indicated for the LAD. Additional arterial grafts may be considered based on practice guidelines.
6. Appropriately sized and accessible target coronary arteries, with a minimum diameter of 1.5 mm and adequate vascular bed (without significant distal stenosis), as assessed by pre-operative cardiac angiography and verified by diameter gauging intraoperatively.

4.2.2. Exclusion Criteria

Patients will be excluded if they meet any of the following:

1. Concomitant non-CABG cardiac procedure.

2. Prior cardiac surgery.
3. Emergency CABG surgery.
4. Contraindication for on-pump CABG with cardioplegic arrest (e.g. severely calcified aorta).
5. Calcification at the intended anastomotic sites, as assessed upon opening of the chest and before randomization.
6. Severe vein varicosity as assessed after vein harvesting and before randomization.
7. History of clinical stroke within 3 months prior to randomization.
8. Severe renal dysfunction (Cr>2.0 mg/dL).
9. Documented or suspected untreated diffuse peripheral vascular disease such as: carotid stenosis or claudication of the extremities.
10. Concomitant life-threatening disease likely to limit life expectancy to less than two years.
11. Inability to tolerate or comply with required guideline-based post-operative drug regimen (antiplatelet plus statin) and/or inability to take aspirin.
12. Inability to comply with required follow-ups including angiographic imaging methods (e.g. contrast allergy).
13. Concurrent participation in an interventional (drug or device) trial.

4.3 Recruitment Strategies

CABG is a prevalent cardiac surgical procedure conducted within the participating Cardiothoracic Surgical Trials Network (CTSN) centers. We will establish enrollment targets for each clinical site based on a review of screening registration form. Enrollment strategies may include mailings to referring physicians of the study hospitals, symposia, and health care events targeted towards this population as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified accrual goals, and additional interventions to facilitate enrollment will be implemented as needed. The Screening Registration form will identify numbers of patients screened and reasons for ineligibility and/or non-enrollment into the trial.

4.4 Inclusion of Women and Minorities

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

- Documentation of the number of women and minorities screened and enrolled via screening registration form;
- Monitoring of such logs from each clinical center on a regular basis;
- If necessary, develop and implement outreach programs designed to recruit adequate numbers of women or minorities.

4.5 Relevance to Medicare beneficiaries

The cohort eligible for participation in this study are all patients with multivessel coronary artery disease scheduled to undergo CABG procedure. From the literature (1,8) we know that CABG patients are typically with a median age of 64-65 years. Hence it is expected that approximately half the patients will be Medicare beneficiaries.

5. Definitions and Measurements of Endpoints and Outcomes

5.1 Primary Endpoint

The primary endpoint is defined as intimal hyperplasia (plaque+media) area [mm^2] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (VEST supported and unsupported) and is measured as a continuous variable.

5.2 Secondary Confirmatory Endpoints

1. *Lumen diameter uniformity* will be assessed by angiography for each graft separately and expressed by the Fitzgibbon classification (22), on a 3-point ordinal scale:
   - I – No intimal irregularity

- II – Irregularity of <50% of estimated intimal surface
- III – Irregularity of >50% of estimated intimal surface

2. *Graft Failure* coded as follows:
0 = Failure = ≥50% stenosis by QCA at 12 months
1 = Success = Otherwise

5.3 Additional Secondary Endpoints

- *Intimal hyperplasia:* (plaque + media) thickness [mm] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (supported and unsupported) and is measured as a continuous variable.
- *TIMI flow grade* assessed by angiography at 12 months on the following 4-point ordinal scale:
  - Grade 0 – No perfusion
  - Grade 1 – Penetration without perfusion
  - Grade 2 – Partial perfusion
  - Grade 3 – Complete perfusion
- *Graft failure* at 12 months, as defined above, separately for right and left territories
- *Repeat revascularization* for supported and unsupported vein grafts (or respective bypassed target coronary artery) over the 5 years of observation
- *Lumen diameter uniformity* expressed by the coefficient of variance (CV) by QCA at 12 months, computed for each graft separately and scored continuously as follows:

$CV_{Uniformity} = SD_{Diameter}/Mean_{Diameter}$

- *Ratio of vein graft lumen diameter to target artery lumen diameter* by QCA at 12 months

5.4 Clinical Events

- Mortality

All-cause mortality will be assessed.

- Hospitalizations
  - Length of Index Hospitalization

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

  - Readmissions

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

- Safety
  - Serious Adverse Events occurring post randomization and up to 12 months after the CABG procedure

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

- MACCE

Major adverse cardiac and cerebrovascular events (MACCE) occurring within 12 months and annually after up to 60 months after the index CABG procedure. MACCE is defined below.

  - All-cause **mortality**;
  - **Stroke** - Defined as any new, rapidly developing focal neurological deficit, lasting longer than 24 hours, ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests, imaging and neurology consultation note). The Modified Rankin Scale and the NIH Stroke Scale must be administered within 24 hours following the event to document the presence and severity of neurological deficits.
    Each neurological event must be subcategorized as:
    - Hemorrhagic stroke
    - Ischemic stroke
    - Other
  - **Myocardial infarction (MI)** – Any one of the following criteria meets the diagnosis of MI

- **Acute MI** - Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the Upper Reference Limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumably new significant ST-T changes or new LBBB;
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy
- **CABG related MI** - defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either
  - New pathological Q waves or new LBBB, or
  - Angiographic documented new graft or new native coronary artery occlusion, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- **Prior MI** – Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence on non-ischemic cause.
  - Pathological finding of prior MI

- **Ischemic driven target vessel revascularization** - (CABG or PCI) of **VEST supported** vein graft or associated target coronary artery.
  Revascularization is considered ischemic driven if the subject has clinical or functional ischemia manifesting in any of the following:
  - **A history of angina pectoris** presumably related to the target vessel
  - **Objective signs of ischemia at rest** (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
  - **Abnormal results of any invasive functional diagnostic test** [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

  The angiography and IVUS procedure performed at 12 months to assess the graft integrity by the study plan will not be counted as MACCE. Clinical evaluation for the 12 months visit will be completed and MACCE will be recorded **prior to** performance of the planned interventional procedure. If revascularization of the VEST supported graft or associated bypassed coronary artery is performed as a result of the angiography, it will be reported and adjudicated according to the definition given above for ischemic driven target vessel revascularization, for assessment of MACCE at time points >12 months.

- *Time to revascularization* for supported and unsupported vein grafts (or respective bypassed target coronary artery). See above definition for revascularization.
- *Revascularization rate* for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years. See above definition for revascularization
- *Time to MI in culprit vessels*, for supported and unsupported vein grafts (or respective bypassed target coronary artery). See above definition for MI
- *Rate of MI in culprit vessels*, for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years. See above for definition of MI.

5.5 Anticipated Adverse Event Definitions and reporting rules

The following complications and adverse events are documented in the literature (5,8) and expected to occur with CABG patients. For the purposes of the trial, in line with IDE and Health Canada regulations, unanticipated adverse device effects (UADE) which are both serious and unexpected (not defined below) and meet the below definition, will be reported by sponsor to FDA/HC and reviewing IRB/REBs. Reports to Health Canada will include adverse device related incidents that occur in Canada that fit the criteria as specified in section 59 of the regulations.

Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB/REB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, HC (even if anticipated) all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

Serious Adverse Event: Serious adverse events (SAEs) are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators or Sponsor. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

UADE is defined in CFR 812.3(s) as: "any serious adverse effect on 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.

Bleeding

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

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

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

Cardiac Arrhythmias

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

Cardiac arrhythmias are classified as follows:

- Cardiac arrest
- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
- Cardiac conduction abnormalities or sustained bradycardia requiring permanent pacemaker placement (includes all PPMs whether associated with a serious AE or not)

Pericardial Fluid Collection

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

Pleural Effusion

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

Pneumothorax

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

Hepatic Dysfunction

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

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

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

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

Major Infection
A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

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

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

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

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

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

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

Heart Failure
Signs of inadequate organ perfusion or congestion, or a syndrome of compromised exertional tolerance manifested by dyspnea or fatigue that requires

- intravenous therapy (diuretics, inotropic support, or vasodilators) and prolongs hospital stay in the judgment of the investigator, or
- introduction of intravenous therapy (diuretics, inotropic support, or vasodilators) at any point following discharge from the index hospitalization, or
- readmission for heart failure

Arterial Non-CNS Thromboembolism
An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

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

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

Revascularization procedure
Revascularizations procedures which occur during the investigation must be reported to Sponsor as soon as possible. Every procedure will be recorded on a Revascularization CRF and the event documented as an adverse event on an Adverse Event CRF.

Other
An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

6. Data Collection Procedures

6.1 Screening and Baseline

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

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

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

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

Release of Medical Information Form
Prior to screening data collection and protocol defined procedures
The patient must sign the Release of Medical Information form or institutional equivalent that authorizes release of medical records, including hospital costing data, to the study Sponsor, investigators and monitors.

Medical History
Within 30 days prior to randomization
This form captures the information pertaining to the medical history including but not limited to previous myocardial infarction, myocardial revascularization, heart failure (NYHA, CCS classifications), stroke, and other comorbidities such as diabetes, hyperlipidemia, and peripheral vascular disease. Information regarding the current medical condition is also captured including but not limited to disposition at time of screening (outpatient, inpatient, ICU, etc.).

Laboratory Assessment
Within 30 days prior to randomization
Creatinine *(mg/dl)* value will be recorded as well as PTT and CK-MB.

Angiography
Within 6 months of randomization
Angiographic data must be available for every candidate patient to assess inclusion criteria. This form captures the date(s) of angiography and all coronary anatomy.

Medications
Within 30 days prior to randomization
This form captures all categories of medications (including but not limited to cardiovascular medications) at one pre-operative time point.

Physical Examination
Within 30 days prior to randomization
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Eligibility Criteria/Eligibility Evaluation Form
Prior to randomization
The inclusion and exclusion criteria will be reviewed and eligibility confirmed by the study team in the operating room just prior to randomization (see section 6.2). The Eligibility Evaluation Form must be completed by the clinical site study coordinator and verified within 48 hours of randomization with a signature and date by the investigator. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Eligibility Evaluation Form. The data collected are HIPAA compliant and include reason for not being randomized.

A representative from the DCC will be available to discuss any questions regarding patient eligibility.

6.2 Randomization

The randomization procedure will be performed inside the OR after confirmation by the surgical team of the patient's eligibility to randomize and performed only after the procedure has reached the stage where all distal anastomoses of the venous grafts have been constructed, to minimize bias and the chance of a randomized patient not participating in the trial. Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system once the checklist of inclusion and exclusion criteria has been completed and verified. For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated.

6.3 Treatment Interventions

All patients enrolled in this trial will undergo surgical CABG. For each patient, two SVG vessels will be assigned to either a VEST-supported or a non-VEST-supported (control) therapy.

All procedures will be performed using a median sternotomy incision, cardiopulmonary bypass support, and cardioplegic arrest. The management of cardiopulmonary bypass and myocardial protection will be at the discretion of the surgeon, using standard techniques.

Coronary Artery Bypass Grafting (CABG)
For the vein graft assigned to control, coronary artery bypass grafting will be performed using standard surgical techniques. Conduit selection and harvesting methods will not be prescribed, except that an IMA will be utilized when an LAD graft is indicated. The technical details of bypass grafting will not be prescribed. Complete revascularization will be performed, within the judgment of the surgical investigator.

Surgical Procedure
Initial surgical intervention
The initial surgical procedure (CABG) must be reported on the surgical procedure form within 48 hours of the event. Operative data such as cross-clamp time, additional procedures performed at the time of the operation, and intra-operative blood transfusions, will also be collected. Data should be collected including but not limited to: procedure details (all grafts performed, venous, arterial, target arteries, graft diameters and lengths, vein harvesting and preservation technique, origin above/below the knee, varicosity), VEST implantation procedure (graft length and diameter assessment, model selection, serial number, technical

success), randomization (time of all distal anastomoses completion, time of randomization, VEST supported graft, control graft), TTFM flow and pulsatility index measurements for all venous and arterial grafts.

6.3.1. Post-operative Medical Management

All patients will be prescribed statins and aspirin per practice guidelines (5) for 12 months. All other routine follow up will be performed in addition to study specifics detailed below.

6.4 Post-Randomization Data Collection

Study Visits

- Peri-operative
- Six weeks post-intervention *(± 2 weeks)*
- Six months post-intervention *(± 30 days)*
- 12 months post-intervention *(± 30days)* preceded by a phone call 6 weeks in advance
- Two, three, four, and five years post-intervention *(± 90 days)*

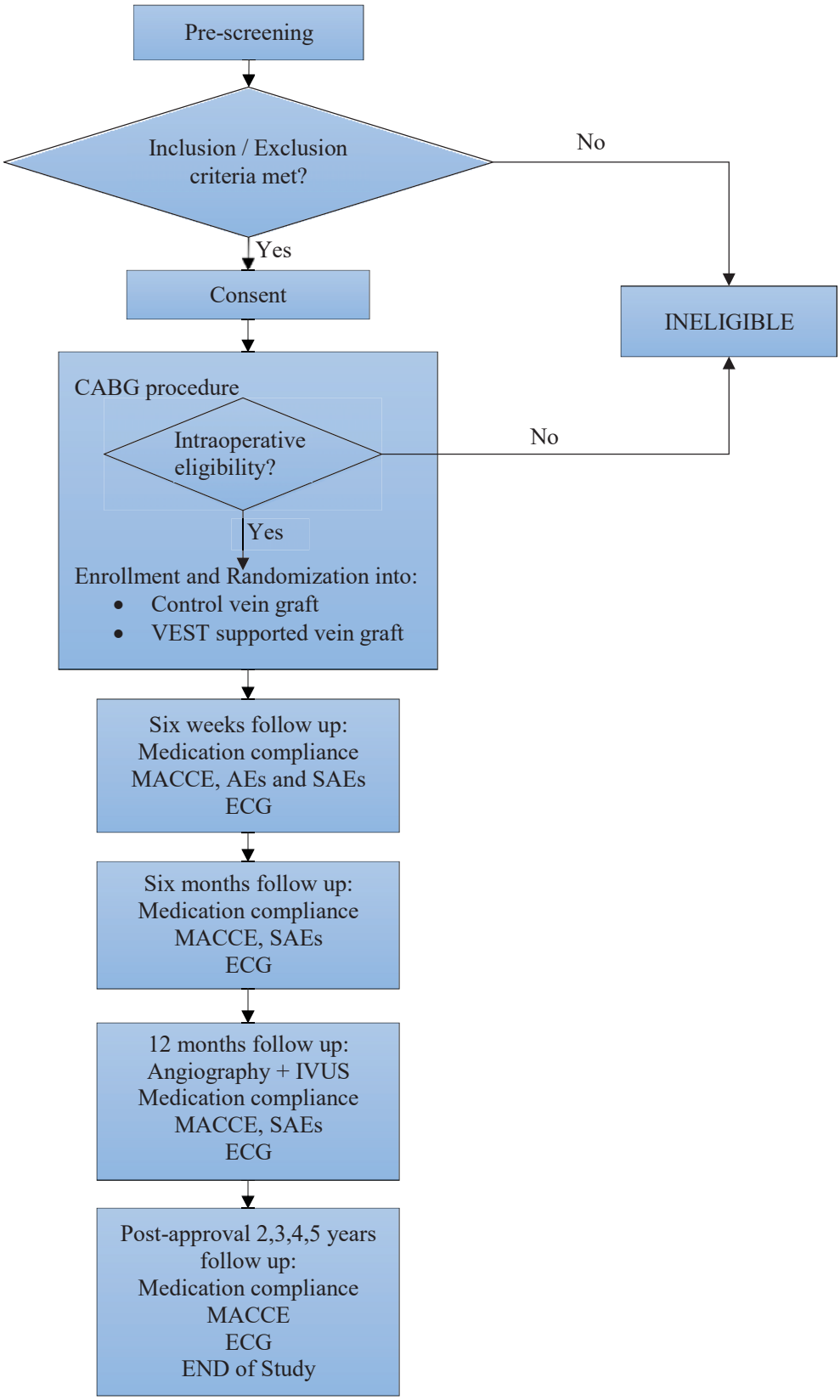

Figure 6: Study flow diagram

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

Medications
At 6 weeks (± 2 weeks), 6 months (± 30 days), 12 months (±30 days) and 2, 3, 4, 5 years (±90 days) post procedure and event-driven
All patients will be prescribed statins and aspirin per practice guidelines [(5)] for 12 months. These and all cardiovascular medications will be recorded at each study visit and also as indicated at the time of associated adverse events.

12 Lead ECG
At 6 weeks (± 2 weeks), 6 months (± 30 days), 12 months (±30 days) and 2, 3, 4, 5 years (±90 days) post procedure and event-driven
ECG results and interpretation will be collected.

Physical Examination
At 12 months (±30 days)
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Coronary angiography
At 12 months (±30 days)
Since this follow-up visit generates the primary endpoint data and completeness of data, each subject will be telephoned 6 weeks before the 1 year post-op date, to be reminded of the upcoming follow up visit and to schedule the appointment.

Coronary angiography – Contrast angiography will be attempted for all grafts and native vessels. Assessment of the patency/stenosis of the vein grafts and treated coronary arteries will be captured.

Coronary Angiography (QCA) by a core lab will be used to analyze data from patent grafts. Data will include Fitzgibbon classification I, II, III), percentage of vessel stenosis, ectatic lesions, blood flow, blood velocity, lumen diameters averaged over 1 mm intervals, TIMI flow grade, Syntax Score of native coronary vessels only.

Intravascular ultrasound (IVUS)
At 12 months (±30 days)
The IVUS catheter will be advanced all the way through each of two study vein grafts (providing patency has been demonstrated by contrast angiography) and pulled back (motorized) at a constant rate.
Images will be recorded and uploaded via the EDC for offline analysis by the independent IVUS core lab.

Event Driven Data Collection
Adverse Events
Event Driven
Detailed information regarding adverse events will be recorded at the time an adverse event becomes known. Relevant source documents and data will be collected including cost data pertaining to MACCE events. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All serious adverse events will be recorded until the patient completes 12 months follow up. MACCE will be collected throughout 60 months post randomization.

AEs are collected up to 6 weeks post procedure, SAEs are collected up to one year, and MACCE are collected for the duration of the study.

Common medical events (as determined by the investigator) such as colds, influenza, elective minor outpatient procedures such as colonoscopy, minor trauma and musculoskeletal discomforts do not need to be collected as adverse events unless they are serious, as defined in section 5.5. Events related to pre-existing

non-cardiac ailments such as arthritis, gout, gastrointestinal reflux disorder do not need to be collected as adverse events unless they are serious as defined in section 5.5.

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

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

Neurologic Dysfunction Assessment
Event Driven
The Modified Rankin Scale (Appendix I) and NIHSS (Appendix II) should be administered by a certified evaluator at the time of a cerebrovascular thromboembolic event (within 72 hours following the event) and at the termination of trial follow-up to document the presence and severity of neurological deficits.

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

Additional Procedures
Event driven
All procedures following the initial study defined surgical intervention must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the operation is to address a complication, the coordinator must also complete an adverse event report.

Collection of procedure data is in line with timelines defined for AE collection above: AEs are collected up to 6 weeks post procedure, SAEs are collected up to one year, and MACCE are collected for the duration of the study.

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

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

Patients reserve the right to withdraw from the study at any time without jeopardy to future medical care. All follow-up assessments and procedures should be performed and recorded up to the time of withdrawal. They may also be administratively withdrawn if they do not return for follow-up visits. If an AE is ongoing at the time of the withdrawal, the treating investigator will attempt to follow the patient until the AE has resolved or stabilized or until follow-up is no longer possible.

If the patient misses a scheduled study visit, the site will attempt to contact the patient to determine and document the reason the patient has failed to return, to obtain any information on medication, adverse events, and to encourage compliance with the study visit schedule.

Investigator's Statement
End of study

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

6.5 End Of Trial

The end of the pivotal trial will be declared when the last patient recruited completes the "12 months" visit. After study completion, patients will be followed by their respective doctors as per standard of care for patients in their condition. Follow-up will continue in the post-approval phase until the last patient reaches 5 year follow-up, as noted above.

6.5.1. Compliance with Protocol

The site Principal Investigator is considered responsible for compliance with the protocol at the investigational site. The Principal Investigator is also responsible for reporting all protocol deviations to the respective IRB and to the DCC. A representative of the DCC will make frequent contact with the Principal Investigator and his/her research staff and will conduct regular monitoring visits at the site to review patient data and device accountability records for compliance with the protocol, e.g., patient eligibility criteria, randomization assignments, device model selection, procedures performed, and follow-up visit schedule.

7. Risk-Benefit Considerations

In all clinical use to date (over 500 patients) the VEST has not been associated with any device related adverse events. The potential benefits of the VEST are in mitigation of vein graft disease parameters such as intimal hyperplasia, lumen non-uniformity and disturbed flow patterns. This potential effect has been observed over a follow up duration of 1 year in a 30 patient pilot study performed in the UK.

The VEST should be implanted by trained professional cardiac surgeons. Care should be taken to use the VEST according to the IFU. The VEST model should be carefully selected according to instructions for use. There is some risk of VEST interfering with side branch ligations or masking kinks in the vein graft, however this can be mitigated with training and careful attention to instructions. Once deployed and expanded on the vein graft, the VEST can, at any time, be recompressed, for inspection and correction of the vein graft, and subsequently re-expanded.

Potentially, if incorrectly placed, the VEST can lead to vein graft failure which in turn can lead to MI or need for additional intervention. This risk can be significantly mitigated by careful model selection, avoidance of metal clips, avoidance of interference with the anastomoses, and careful compliance with the IFU.

Additional potential adverse effects associated with the VEST may include the complications reported for conventional coronary artery bypass grafting procedure such as: vein graft failure, MI, stroke, ventricular fibrillation, impaired cardiac rhythm, infection, bleeding, death, or need for repeat revascularization.

In summary, while the potential benefits in mitigating vein graft disease are promising, the risks are mainly due to those associated with any CABG surgery and the adjunct use of the VEST ads minimal risk which can be mitigated with careful training and compliance with IFU.

Other risks associated with coronary artery disease and/or major surgery, such as CABG, apply to these patients, but are not expected to be influenced by use of the VEST.

8. Statistical Considerations

8.1 General Design Issues

This study is a prospective, multi-center, randomized clinical trial that will enroll patients with multi-vessel disease undergoing CABG. The novel VEST treatment will be randomly assigned with equal probability to either a right or left and/or short or long vein graft within each patient. The nature of the treatments precludes masking of treating clinicians to treatment assignment; however, investigators will be masked to data from other clinical sites with the exception of reportable UADE: serious, unanticipated device related or possibly related AEs, which must be revealed for IRB/REB -reporting purposes. The trial's primary aim is to determine whether the VEST device is safe and effective for its intended use in supporting saphenous vein grafts used as conduits in patients who undergo CABG for coronary arteriosclerotic disease.

The within-patient design takes advantage of the positive correlation between intimal hyperplasia (IH) measured on grafts within the same patient, to produce a less variable measure of treatment difference, and so increase power compared to between-patient designs.

8.2 Analysis Sets

8.2.1. Safety Analysis Set

The safety analysis set will consist of all patients who are considered enrolled in the study, once they are randomized and an identification code is generated.

Handling of missing data: Only observed values will be used to analyze safety data; i.e. missing safety data will not be imputed.

8.2.2. Full Analysis Set

The full analysis set (FAS) will, consistent with ICH Guideline E9 (35), include all randomized vessels for whom the study procedure was initiated in either arm according to the intent-to-treat (ITT) principle.

8.3 Sample Size Justification

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing CABG. The primary endpoint of the study will be the intimal hyperplasia (plaque + media) area [mm^2] as assessed by IVUS at 12 months post randomization. Sample size is based on the assumption that IH will be normally distributed with standard deviation of 1.7 mm^2 in both the VEST supported and the unsupported vessels. We also assume that the mean IH in the unsupported vessel is 5.1 mm^2 and that the correlation between IH measured on grafts within the same patient is equal to 0.5. In addition, we anticipate that approximately 13% of patients will have the supported and/or unsupported grafts occluded or severely stenosed and so unable to have IH measured through IVUS; in approximately 50% of these patients IH will not be obtained in either graft, while in the rest, the occlusion will only affect one of the two graft, in 25% the VEST graft will be occluded and in 25% the control graft will be occluded). Although it is unclear to what extent occlusion is related to IH one year post CABG, we will treat missing values of IH resulting from occluded vessels as non-ignorable missing (see below section) using an imputation model that will penalize these vessels and will reduce the effect size. Therefore, we assume a conservative effect size of 0.4 mm^2, or a reduction of IH in the VEST vessels compared to the control vessel of about 8%.

Under these assumptions, fixing the power at 90% we need to enroll 190 patients, before adjustment for loss to follow-up.

Lost to follow up and refusals: The term “lost to follow-up” is used to describe an individual who has withdrawn consent to be in the study or who can no longer be located or assessed. Such individuals represent those for whom primary outcome assessment is no longer possible. We anticipate that the loss to follow-up rate or refusal to perform an IVUS in this study will be around 15%. To account for this loss to follow up rate a total of 224 eligible participants will be enrolled in the study.

8.4 Randomization Design and Procedure

Randomization will be performed only after the procedure has reached the stage where all distal anastomoses of venous grafts have been constructed. Subjects will be block randomized by territory and/or by SVG length.

If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will assign the treatment and control vessel by their lengths.

Only grafts originating proximally from the aorta will be considered for randomization. Sequential grafts will not be included in the study. Where more than one graft may be performed per territory, the vein grafts will be uniquely distinguished by their pre-measured length as “Longest” and “Shortest”.

8.5 Statistical Analysis

8.5.1. Overview

Data will be summarized in tables using descriptive statistics (mean, standard deviation, median, minimum, maximum and number of subjects) for continuous data, or in frequency tables for categorical data. Tables will be presented by study arm and overall. Data listing by subject will be provided.

8.5.2. Subject Disposition

Subject disposition will be tabulated; the number of enrolled, exposed, prematurely terminated and completed subjects will be summarized, including the number of subjects in each analysis population.

A list of dropouts will be prepared including reason for discontinuation, and time of discontinuation.

8.6 Analysis of the primary endpoint

The primary outcome is the degree of intimal hyperplasia at 12 months post-surgical intervention, assessed by IVUS. The null hypothesis is that there is no difference in the 12-month intimal hyperplasia between vessels randomized to the VEST compared to control vessels. The primary null hypothesis will be tested in an intent-to-treat analysis using a two-tailed 0.05 alpha level. The analysis will be conducted using a Wilcoxon signed-rank test. A multiple imputation approach will be used to impute the intimal hyperplasia values of the occluded vessels as described below. In addition, we will also account for the occluded vessels in the computation of the Wilcoxon sign-rank test as follows. If two vessels in the same individual are both occluded, we will assign an absolute value of zero for the difference between the two scores irrespective of the imputed values. Pairs with a value of zero will be excluded from the computation of the test statistic as usual for the Wilcoxon rank-sign test. If only one of the two vessels is occluded in the same individual, then we will assign an absolute value equal to the difference between the observed and the imputed score. The sign associated with the rank for this difference, however, will be in favor of the non-occluded vessel. If both vessels are not occluded they will be treated as usual in the computation of the Wilcoxon sign-rank test.

We anticipate that roughly 13% of vessels will be obstructed and unsuitable for IVUS, and thus intimal hyperplasia will be measured only on non-obstructed vessels. Although the degree of intimal hyperplasia may be independent of the mechanism of obstruction, we will consider an obstructed vessel as a failed vessel in the analysis. Specifically, we will assume a non-ignorable mechanism (not missing at random or NMAR) for the data missing due to obstructed vessels.

We will address the problem of missing IVUS data by multiple imputation — i.e., creating several potential imputed observations for each missing data using a predictive modeling (36). The underlying model will use the pattern-mixture approach, which posits a separate distribution of the true IVUS measurement for missing and non-missing observations. The model will include the following subject specific covariates: hypertension, diabetes, hyperlipidemia, and smoking status; and the following vessel specific covariates: treatment assignment, coronary territory, vein harvest and preservation techniques.

Let Y represent the continuous outcome variable (i.e. intimal hyperplasia) and let R be an indicator variable that assumes different values according to whether Y is observed or missing. Under a pattern-mixture model, the joint distribution of the outcome Y and the missing indicator variable R, $f(Y,R)$, is factorized into the density of the outcome, conditional on the pattern of missingness of Y, $f(Y|R)$, and the marginal distribution of the missing indicator variable, $P(R)$.

$$f(Y,R)=f(Y|R)P(R)$$

In longitudinal studies, the probability distribution $P(R)$ refers to the probabilities of the different possible patterns of missingness. In this situation we distinguish only two patterns of missing data: we define a case to be complete $(R=1)$ if a vessel is able to be evaluated at follow-up, and to be incomplete $(R=0)$ if the follow-up measurement is missing due to occlusion.

Under the NMAR framework, the density $f(Y|R)$ is specified differently depending on whether $R=0$ (Y is missing) or $R=1$ (Y is observed), reflecting the fact that the missing values may come from a different distribution than the observed ones. In this study, we will assume that the distribution function of intimal hyperplasia is normal, with $f(Y|R=1)\sim N(\mu, \sigma^2)$ for the observed data and $f(Y|R=0)\sim N(\mu+\delta, \gamma\sigma^2)$ for the missing data. The parameters δ and γ are sensitivity parameters. In order to "penalize" the obstructed vessels we will assume that δ is positive to reflect, on average, larger values of intimal hyperplasia. Specifically, we will assume that the non-observed values come from a normal distribution with mean equal to the 90th percentile of the distribution of intimal hyperplasia in the VEST I trial, which was equal to 6.84 mm^2.

The procedure will be implemented in two stages: First we will create of a set of imputations for intimal hyperplasia for each patient with missing data due to an occluded vessel. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. Characteristics of the vessels, like laterality and length as well as patients' characteristics will be used to inform the predictive models. This corresponds to the usual imputation under a missing at random (MAR) mechanism. In the second stage, values will be generated from a prior distribution $N(\delta, \sigma_\delta^2)$, where δ is such that $\delta+\mu$ is equal to the 6.84 mm^2, and added to the imputed response from the first stage.

We will repeat the imputation process 30 times to achieve maximal stability of the procedure. Following Rubin, we will conduct a separate analysis for each completed dataset using a Wilcoxon signed-rank test as described above. Li et al (37) method of combining the significance levels from the 30 analyses will be used to test the mean difference between the intimal hyperplasia of the treated and control vessels.

For simplicity our primary analysis will not be stratified by clinical center, although the randomization will stratify by clinical center. This should result in only a small loss of efficiency.

Sensitivity Analysis

We will conduct a series of sensitivity analyses to determine the stability of the estimate of the treatment effect obtained with the multiple imputation pattern-mixture approach. Specifically, we will work with different values of the sensitivity parameter δ and γ to determine how our assumptions about the distribution of the missing data influence the results. For example, assuming $\delta = 0$ corresponds to a missing-at-random (MAR) assumption, which posits that there is no information in the fact that a vessel is occluded and therefore cannot be measured. These analyses will allow us to determine how large δ has to be to change the outcome of the final analysis with respect to statistical significance of the treatment effect.

Crossovers

Vessels randomized to VEST but not supported will be considered crossovers. Similarly, vessels randomized as control but VEST supported will be considered cross-overs. We anticipate very few cross-overs in this trial. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect of on trial outcomes.

Missing Data due to Missed Visits

Patients will be scheduled for a 12-month IVUS study, and patients should be carefully screened prior to randomization regarding their willingness to undergo an IVUS study. Despite this screening and ongoing communication with patients regarding the importance of study endpoint assessment, we anticipate that there will be 10-15% missing primary endpoint assessments. Patients missing primary endpoint assessments due to loss to follow-up are accounted for in the sample size calculation.

8.7 Analysis of Secondary Confirmatory Endpoints

Following are the study's two secondary confirmatory hypotheses that will be tested in FAS in the order presented using a sequential strategy:

Secondary Confirmatory I

H_0: $(\text{Lumen Diameter Uniformity})_{VEST} = (\text{Lumen Diameter Uniformity})_{SOC}$

H_1: $(\text{Lumen Diameter Uniformity})_{VEST} \neq (\text{Lumen Diameter Uniformity})_{SOC}$

Where lumen diameter is measured using Fitzgibbon classification (scale of 1 to 3) as described in Section 5.2.

Hypotheses will be tested using the Wilcoxon Sign-rank test with two-sided Alpha = 0.05. We will declare success on this endpoint if we will have succeeded on the primary efficacy endpoint and rejected the null hypothesis in this section as a result of mean rank for VEST being lower than SOC.

[that is: (Lumen Diameter Uniformity)VEST > (Lumen Diameter Uniformity)SOC].

Secondary Confirmatory II

H_0: $(\text{Graft Failure})_{VEST} = (\text{Graft Failure})_{SOC}$

H_1: $(\text{Graft Failure})_{VEST} \neq (\text{Graft Failure})_{SOC}$

Where graft failure ("yes" or "no") is determined as described in Section 5.2.

Hypotheses will be tested using McNemar's test for paired binary observations with two-sided alpha = 0.05. We will declare success on this endpoint if we will have succeeded on both confirmatory endpoints. [that is: (Lumen Diameter Uniformity)VEST > (Lumen Diameter Uniformity)SOC AND (Graft Failure)VEST <(Graft Failure)SOC].

8.8 Analysis of Additional Secondary Endpoints

The following additional secondary endpoints will be analyzed:

Intimal hyperplasia: (plaque + media) thickness [mm] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (supported and unsupported) and is measured as a continuous variable. This secondary endpoint will be analyzed using mixed models with patients as random effects.

TIMI flow grade assessed by angiography at 12 months on the following 4-point ordinal scale:

- Grade 0 – No perfusion
- Grade 1 – Penetration without perfusion
- Grade 2 – Partial perfusion
- Grade 3 – Complete perfusion

This secondary endpoint will be analyzed using a Wilcoxon signed-rank test.

Graft failure at 12 months, as defined above, separately for right and left territories. This endpoint will be analyzed using McNemar's test for binary observations.

Repeat revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) over the 5 years of observation. This endpoint will be analyzed using McNemar's Test for paired 2 x 2 tables.

Lumen diameter uniformity expressed by the coefficient of variance (CV) by QCA at 12 months, computed for each graft separately and scored continuously as follows:

$CV_{Uniformity} = SD_{Diameter}/Mean_{Diameter}$

Ratio of vein graft lumen diameter to target artery lumen diameter by QCA at 12 months.
The latter two endpoints will be analyzed using mixed-effect models with patient as random intercept.

8.9 Clinical Events

The clinical events will be tabulated and characterized using descriptive statistics. Time to death will be described using a Kaplan-Meier curves, adverse events (including MACCE) will be described as rates and proportions. 95% confidence intervals will be constructed around the point estimates.

8.10 Interim Analysis

There is no planned interim analysis.

8.11 Five-year Follow-up

Patients participating in this trial will be followed for an additional 4 years after completing the 12-month pivotal trial to assess the following endpoints:

- Revascularization rate for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years.
- Rate of MI culprit vessels, for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years.
- Time to revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery).
- Time to MI in culprit vessels, for supported and unsupported vein grafts (or respective bypassed target coronary artery).

Rates at 3 and 5 years will be analyzed by Fisher's exact test. Time-to-event endpoints will be described using Kaplan-Meier curves and analyzed using the Cox Proportional hazards model—with and without adjustment for individual covariates. While these analyses are pre-specified in the protocol, this study is not powered for these endpoints.

9. Data Collection, Study Monitoring, and Data Disclosure

9.1 Data Management

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

Record and Electronic Signatures, the FDA's "Guidance: Computerized Systems Used in Clinical Trials, and the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Quality Assurance

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

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data and/or values that are outside the range of what is typically considered to be physiologically possible). Monitors will enter these queries through the EDC system for site coordinators to either correct or verify.

9.2 Study Monitoring and Source Data Verification

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

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

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

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

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

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

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

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

10. Organization of the Study

This section describes the overall study organization. The study is conducted in the clinical centers who participate in the Cardiothoracic Surgical Trials Network (CTSN). The trial is sponsored by VGS. The following committees and institutions will be involved in the administration of the study.

10.1 Event Adjudication Committee (EAC)

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all serious adverse events and causes of mortality. The individuals who will serve on the committee have no formal involvement or conflict of interest with the clinical trial or the DCC, and will be appointed by the DCC. The committee will consist, at least, of a cardiothoracic surgeon, a cardiologist, and a neurologist. The EAC will meet 8 times annually or as needed to review outcomes data for each subject enrolled.

10.2 Data and Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians, biostatisticians, ethicists, neurologists and bioengineers who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC, or the clinical sites. The DSMB will act in a senior advisory capacity to the DCC and VGS regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events and mortality. They will communicate their findings directly with the DCC. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

10.3 Clinical and Data Coordinating Center (DCC)

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

10.4 IVUS/Coronary Angiography Core Lab

The Coronary Angiography Core Lab, Mount Sinai Intravascular Imaging Core Laboratory of Icahn School of Medicine at Mount Sinai (1450 Madison Ave, New York, NY), is directed by Dr. Jagat Narula. All angiograms and intravascular ultrasounds will be performed according to a standardized protocol (see Manual of Operations) and will be centrally analyzed.

10.5 Site Qualification

The study will be conducted in up to 20 clinical centers participating in the Cardiothoracic Surgical Trials Network (CTSN). Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the Data Coordinating Center and Sponsor with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile

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

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in CABG. To qualify as a surgeon participating in this trial, the surgical investigator must have performed at least 20 on pump CABG procedures annually averaged over two years as an attending surgeon.

Cardiology investigators will have expertise in diagnostic angiography and IVUS and must have performed at least 10 procedures annually averaged over two years as an attending cardiologist.

Surgical physicians' assistants (PA) or nurse practitioners (NP) must have performed at least 20 vein graft harvest procedures annually averaged over two years since licensure.

Surgeon and cardiologist training for VEST
The surgical investigator, PA and/or NP will receive onsite training from the VGS representative. All cardiology investigators will receive an acquisition protocol for the angiography and IVUS.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

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

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

Site Approval
The following documents must be collected prior to site approval and opening to patient enrollment:

- FDA IDE approval
- Signed Clinical Study Agreement with Vascular Graft Solutions, Ltd.
- Signed investigator agreement as approved in IDE G150225
- Signed Conflict of Interest Statements
- Completed Delegation of Authority Log
- Signed and dated CVs for all staff on Delegation of Authority Log
- Privacy training (HIPAA) and Human Subjects training documentation (as required by local institutional guidelines) for all staff on Delegation of Authority Log
- Current licenses for all staff on Delegation of Authority Log
- NIH Stroke Scale and Modified Rankin Scale Training Certification for delegated staff
- IRB roster
- IRB approval for protocol, informed consent document, HIPAA authorization
- Clinical Center Laboratory Certification
- Laboratory Normal Ranges
- Surgical Certification forms for Surgeons
- Cardiology Certification for Cardiologist
- NP/PA Certification forms
- Surgeon, NP/PA VEST training documents
- Signed Document Approval Form for protocol
- Study-specific training documents

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

10.6 Patient Confidentiality

All patients' records will be kept confidential according to HIPAA guidelines. Study Investigators, Sponsor representatives, site IRBs, the DCC, EAC, medical monitors, FDA and NHLBI personnel may review source

documentation as necessary but all unique patient and hospital identifiers will be removed from source documents which are sent to the DCC and/or Sponsor. The aggregate data from this study may be published as per publication policy documented in the CTA; however, no data with patient identifiers will be published.

10.7 Publications

The Sponsor and CTSN investigators plan to publish the outcomes of this study. Publication in writing and/or orally will take place after completion of the 1 year data collection and analysis or sooner if the study is terminated. Publication arrangements are detailed in the CTA.

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12. APPENDIX I: MODIFIED RANKIN SCALE (MRS)

Instructions: Assessment should be completed by a certified evaluator.

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

☐	0=	No symptoms at all
☐	1=	No significant disability, despite symptoms; able to carry out all usual duties and activities
☐	2=	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
☐	3=	Moderate disability; requiring some help, but able to walk without assistance
☐	4=	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
☐	5=	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

13. APPENDIX II: NIH STROKE SCALE(NIHSS)

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

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

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

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

1. Level of Consciousness

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

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

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

1c. LOC Commands
Say to the patient "open your eyes...now close your eyes" and then "Make a fist...now open your hand". Use the non-paretic limb. If amputation or other physical impediment prevents the response, use another suitable one step command. The priming phrase is not scored, and these are used only to set the eyes or hand in a testable position. That is, the patient may be asked first to open the eyes if they are closed when you begin the test. Scoring is done on the second phrase "close your eyes". Count the number of incorrect responses and give credit if an unequivocal attempt is made to perform the operative task, but is not completed due to weakness, pain or other obstruction. Only the first attempt is scored and the questions should be asked only once.

2. Gaze

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

3. Visual Fields

Visual fields are tested exactly as demonstrated in the training video. Use finger counting or movement to confrontation and evaluate upper and lower quadrants separately. A score of 3 is reserved for blindness from

any cause, including cortical blindness. A score of 2 is reserved for a complete hemianopia, and any partial visual field defect, including quadrant anopia, scores a 1.

4. Facial Movement (Facial Paresis)

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

5. Motor Arm-Right

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

Motor Arm-Left

See explanation of 5.

6. Motor Leg-Right

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

Motor Leg-Left

See explanation of 6.

7. Limb ataxia

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

Please indicate presence of ataxia in arms and legs.

8. Sensory

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

9. Best Language

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

10. Dysarthria

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

11. Extinction and Inattention (formerly Neglect)

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

Total Score: Please provide the total score for the subject as determined by the 11 categories of questions. Do not include scores of "9" in total.

Protocol number	CD0131
Study title	A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support
Sponsor	Vascular Graft Solutions Inc. c/o Broadview Ventures 265 Franklin Street, Suite 1902 Boston, MA 02110 Phone: 617.341.8121
VEST Manufacturer	Vascular Graft Solutions Ltd. (VGS) 24 Raoul Wallenberg St. Tel Aviv, Israel 6971921 Tel: +972-3-5499054 Fax: +972-3-6024966
Sponsor Contact	Orit Yarden, PhD Mobile: +972-54-3073050 orit@graftsolutions.com
Clinical and Data Coordinating Center (DCC)	International Center for Health Outcomes and Innovation Research (InCHOIR) Coordinating Center for the Cardiothoracic Surgical Trials Network (CTSN) Icahn School of Medicine at Mount Sinai New York

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Sponsor in confidence and.

I have read this protocol in its entirety and I agree to all aspects.

_____	_____
Investigator printed name	Site
_____	_____
Signature	Date

RETURN TO SPONSOR WITH THE ATTACHED PROTOCOL

CONTENTS

Definitions, Acronyms & Abbreviations

21CFR	Code of Federal Regulation number 21
AE	Adverse event
CABG	Coronary artery bypass grafting
CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CFR	Coronary Flow reserve
CK-MB	Creatine Kinase-Muscle/Brain
CV	Coefficient variance
CT	Computed tomography
CTSN	Cardiothoracic Surgical Trials Network
Cr	Creatinine
CRF	Case report form
cTn	Cardiac troponin
COVID-19	Coronavirus Disease 2019
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture system
FDA	Food and Drug Administration
FFR	Fractional Flow reserve
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IABP	Intra-aortic balloon pump
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IFU	Instructions for use
IRB	Institutional Review Board
IVUS	Intra vascular ultrasound
LAD	Left anterior descending coronary artery
LBBB	Left bundle branch block
LIMA	Left internal mammary artery
LOS	Length of stay
iMA	Internal mammary artery
MACCE	Major adverse cardiac and cerebrovascular events
MI	Myocardial infarction
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NP	Nurse Practitioner
NYHA	New York Heart Association
PA	Physician's Assistant
PCI	Percutaneous coronary intervention
PI	Pulsatility index
PMA	Premarket approval
PTT	Partial Thromboplastin Time
SAE	Serious adverse event
SMC	Smooth muscle cell
SOC	Standard of care
SOP	Standard operating procedure
SVG	Saphenous vein graft
QCA	Quantitative coronary angiography
TIMI	Thrombolysis in myocardial infarction
TTFM	Transit time flow measurement
UADE	Unanticipated adverse device effect
URL	Upper reference limit
VEST	Venous external support
VGS	Vascular Graft Solutions Ltd.

Synopsis

STUDY TITLE	A multi-center, randomized, within-subject-controlled, open label study of the safety and effectiveness of VEST, Venous External Support
STUDY	VEST™ Venous External Support
TREATMENT PHASE	Pivotal study under an Investigational Device Exemption (IDE) Primary endpoints at 12 months will be used to support a PMA application. Long term data, up to 5 years follow-up, will be monitored in the post-approval period.
CLINICAL SIGNIFICANCE	Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease. Despite the proposed benefits of multiple arterial grafts, autologous saphenous vein grafts (SVGs) are still the most frequently used bypass conduits in CABG. Progressive SVG failure after CABG remains a key limitation to the long-term success of surgery.
OBJECTIVES	To demonstrate the safety and effectiveness of the VEST for its intended use: Limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease.
STUDY DESIGN	Prospective, multi-center, randomized, within-subject-controlled , trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison between two sets of SVGs: A VEST supported set; and an unsupported set.
ENDPOINTS	Primary endpoint: Intimal hyperplasia (plaque+media) area [mm^2] as assessed by IVUS at 12 months. Occluded vessels are accounted for in the analysis of the primary endpoint. Secondary confirmatory endpoints: 1. Lumen diameter uniformity, assessed by angiography for each graft separately and expressed by the Fitzgibbon classification (22), on a 3-point ordinal scale: I – No intimal irregularity II – Irregularity of <50% of estimated intimal surface III – Irregularity of >50% of estimated intimal surface 2. Graft Failure (≥50% stenosis) by cardiac angiography at 12 months Clinical Events 1. Serious adverse events 2. MACCE 3. Mortality 4. Hospitalization
RX ARMS	In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Patients will be block randomized by territory and/or by SVG length. If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will randomly assign the treatment and control vessels by their lengths.

COHORT	Sample size 224 subjects will be enrolled in this trial. Inclusion criteria 1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation. 2. Age 21 years or older. 3. Planned and scheduled on-pump CABG. 4. Two or more vein grafts to native vessels having at least 75% stenosis and comparable runoff. 5. IMA graft indicated for the LAD. Additional arterial grafts may be considered based on practice guidelines. 6. Appropriately sized and accessible target coronary arteries, with a minimum diameter of 1.5 mm and adequate vascular bed (without significant distal stenosis), as assessed by pre-operative cardiac angiography and verified by diameter gauging intraoperatively. Exclusion criteria 1. Concomitant non-CABG cardiac surgical procedure. 2. Prior cardiac surgery. 3. Emergency CABG surgery. 4. Contraindication for on-pump CABG with cardioplegic arrest (e.g., severely calcified aorta). 5. Calcification at the intended anastomotic sites, as assessed upon opening of the chest and before randomization. 6. Severe vein varicosity as assessed after vein harvesting and before randomization. 7. History of clinical stroke within 3 months prior to randomization. 8. Severe renal dysfunction (Cr>2.0 mg/dL). 9. Documented or suspected untreated diffuse peripheral vascular disease such as: carotid stenosis or claudication of the extremities. 10. Concomitant life-threatening disease likely to limit life expectancy to less than two years. 11. Inability to tolerate or comply with required guideline-based post-operative drug regimen (antiplatelet plus statin) and/or inability to take aspirin. 12. Inability to comply with required follow-ups including angiographic imaging methods (e.g. contrast allergy). 13. Concurrent participation in an interventional (drug or device) trial.
DATA AND SAFETY MONITORING	An independent Data and Safety Monitoring Board (DSMB) will oversee patient safety and overall progress of the study. An independent Event Adjudication Committee (EAC) will review and adjudicate adverse events occurring during this trial. Stopping guidelines for safety will be developed based upon trial data.
DURATION	Accrual is expected to take 12 months, and all patients will be followed for the primary endpoint at 1 year post-randomization, with annual visits until 5 years post-randomization

Data Collection Schedule

Assessment	Screening/ Baseline	Intra-Op	6 Weeks	6 Months	12 Months	Years 2,3,4,5
Visit Windows	w/in 30 days		+/- 2 weeks	+/- 30 days	+/- 30 days	+/- 90 days
General						
Informed Consent	X					
Release of Medical Information	X					
Screening Log and Registration	X					
Medical History	X					
Laboratory Assessment	X					
Medications	X		X	X	X	X
Physical Exam	X				X	
ECG	X		X	X	X	X
Phone call to subject					X (6 weeks prior to 1 year post-op date)	
Coronary Angiography[1]	X				X	
Eligibility Criteria	X					
Intravascular Ultrasound					X	
Randomization[2]		X				
Surgical Procedure		X				
TTFM data		X				
Event Driven Data						
Adverse Events		X	X			
Serious Adverse Events		X	X	X	X	
MACCE		X	X	X	X	X
COVID-19[3]					X	X
Procedures		X	X	X	X	X
Hospitalization	X	X	X	X	X	X

[1] Angiography at screening must be within 6 months

[2] The randomization procedure will be performed inside the OR after confirmation by the surgical team of the patient's eligibility

[3] A confirmed diagnosis of Coronavirus disease 2019 (COVID-19)

1. Objectives

The purpose of this study is to demonstrate the safety and effectiveness of the VEST for its intended use: limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting (CABG) procedures as treatment for coronary arteriosclerotic disease.

This protocol describes a prospective, multi-center, randomized, within-subject-controlled, open label clinical trial to evaluate the safety and effectiveness of the VEST, an external mechanical support for autologous saphenous vein grafts that are created during Coronary Artery Bypass Surgery (CABG).

This study is designed to provide safety and effectiveness data with the primary endpoint measured over 12 month follow up post index CABG procedure. Patients will continue to be followed annually up to 5 years in the post-approval period.

2. Background and Rationale

2.1 The Clinical Need

Coronary artery bypass grafting (CABG) remains the gold standard treatment for patients with multi-vessel coronary artery disease (1). Despite the proposed benefits of multiple arterial grafts (2), autologous saphenous vein grafts (SVGs) are still, numerically, the most frequently used bypass conduits in CABG. However, progressive SVG failure after CABG remains a key limitation to the long-term success of surgery (3, 4). As many as 25% of SVGs occlude within 1 year of CABG; an additional 1-2% occlude each year during the 1 to 5 years after surgery; and 4% to 5% occlude each year between 6 and 10 years postoperatively. Therefore, 10 years after CABG, 50% to 60% of SVGs are patent, only half of which are disease free (5).

Intimal hyperplasia and subsequent SVG failure have significant effects on clinical outcomes such as onset of angina, need for revascularization intervention (surgical or percutaneous), myocardial infarction (MI), and death. The localized areas of "adaptive" intimal hyperplasia that occur in native human arteries have been defined by the American Heart Association Council on Arteriosclerosis as "atherosclerosis-prone regions" (6). FDA recognizes mitigation of intimal hyperplasia as the main effect mode of the drugs eluted by coronary stents (7). In a similar process the extensive intimal hyperplasia throughout the length of a vein graft may effectively create a diffuse atherosclerosis-prone region (4).

The pathophysiology of SVG failure is a well-documented consequence of several intrinsic and extrinsic factors (3, 4). Beyond short-term factors and technical surgical errors, stenosis and failure is dominated by proliferation of intimal hyperplasia which is the foundation for graft atheroma and subsequent vein graft failure, ultimately resulting in higher rates of coronary re-intervention (stenting or re-do CABG), stroke, MI and death in patients with failed SVGs.

Several factors contribute to SVG failure in the short term. Even under optimal conditions, saphenous vein harvesting results in endothelial cell loss, damage to medial smooth muscle cells (SMC), and disruption of micro-perfusion to the vessel wall (10).

Following implantation into a vigorous arterial circulation system, saphenous veins may experience abrupt hemodynamic changes with increased blood pressure, shear stress, wall tension, and pulsatile flow (11,12,13). Among these, high circumferential wall stress and low wall shear stress coupled with intraluminal irregularities are the dominant promoters of vein grafts stenosis (14,15).

Evidence from experimental studies has indicated a strong causal relationship between increased circumferential wall stress and activation of various intracellular signaling molecules (15). These chains of events stimulate vascular smooth muscle cells proliferation and migration in the media, accelerating the progression of intimal hyperplasia. From the standpoint of hemodynamic adaptation, the ratio of lumen radius to wall thickness in vein grafts tends to approach the same value as that in run-off arteries for maximum efficiency of blood transportation. Accordingly, structural remodeling of the venous lumen and wall occurs (13). An external vein graft support has the ability to limit abrupt dilatation and associated wall stretch, reinforce the venous wall thus absorbing pressure, and subsequently mitigate and suppress the proliferative reaction induced by high wall stress.

In addition to significant effects on the vein graft wall, the arterialization of the vein graft results in disturbed and turbulent flow patterns within the vein grafts. The irregular remodeling and dilatation result in a non-uniform lumen which in turn results in disturbed turbulent and oscillatory flow which in turn promote

atherogenesis (16). The geometric diameter mismatch between artery and vein also results in flow discrepancies (13,14). An external vein graft support such as the VEST is designed to regulate flow patterns by enhancing lumen uniformity.

Over the longer term, proliferation of intimal hyperplasia renders the vein graft lumen vulnerable to atherosclerosis leading to SVG stenosis and occlusion (17,18,19,20,21).

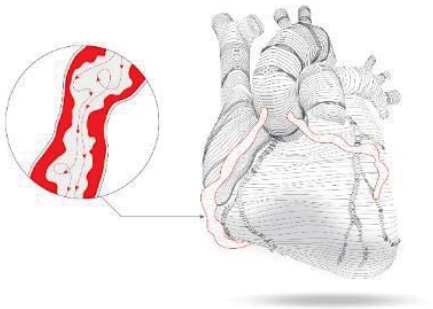

Figure 1: Vein graft remodeling flow disturbances

2.2 Perivascular External Support

Attempts to mitigate intimal hyperplasia and SVG failure have been the focus of intense clinical research. Pharmacological attempts, including Edifoligide (8) and aspirin + clopidogrel (9), have both failed to reduce SVG failure or mitigate intimal hyperplasia, respectively at 12-18, months after CABG.

Mechanical external supports for SVGs have shown considerable promise in pre-clinical testing with reduction of vessel dilatation and stretch, proliferative intimal hyperplasia and medial thickening (24, 25, 26, 27, 28). External support also reduces the diameter mismatch between the vein graft and the host coronary artery and increases the lumen uniformity (29). Furthermore, external stents have been shown to facilitate adventitial neovascularization that counteracts damage to the vein graft's vasa vasorum during harvesting (30, 31). However, limited clinical data has been published to date with such devices and adoption into clinical practice is lacking. In two randomized self-controlled studies of other devices intended to provide permanent support to SVGs, Murphy et al (32) describe 100% occlusion of supported SVGs at six months and Schoettler et al (33) report a 72% occlusion rate at nine months. Both these external stents (Figure 2) required gluing and/or suturing to the vein graft in order to optimize length and diameter match and to prevent migration, which may explain their lack of success.

The eSVS Mesh described in Schoettler et al (33) requires both application of fibrin glue and suturing the anastomoses through the device mesh. The anastomoses are probably the most sensitive part of the CABG procedure and are the most prone to technical errors. In addition, the application of fibrin glue on vein grafts has been tested in-vivo in a porcine model and has been histologically shown to induce an increase of graft thickening (34) and may contribute to vein graft failure (33). This is of course counterproductive to the attempts of external support devices to inhibit graft remodeling.

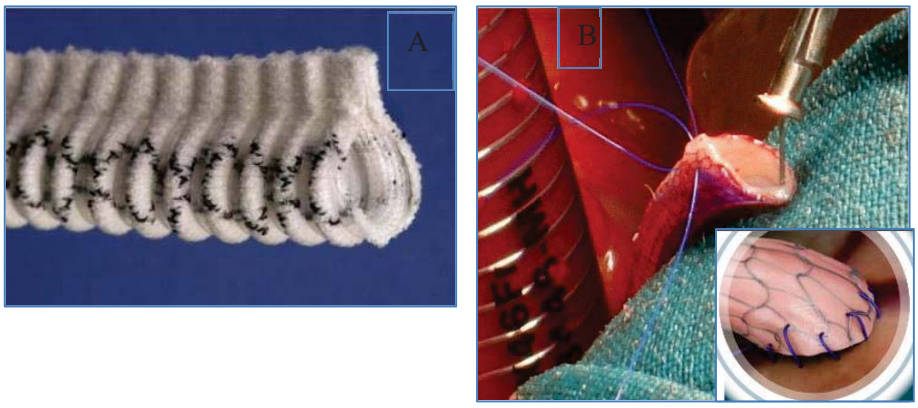

Figure 2: A: Extent external support (Schoettler et al); B: eSVS MEsh esternal support (Murphy et al)

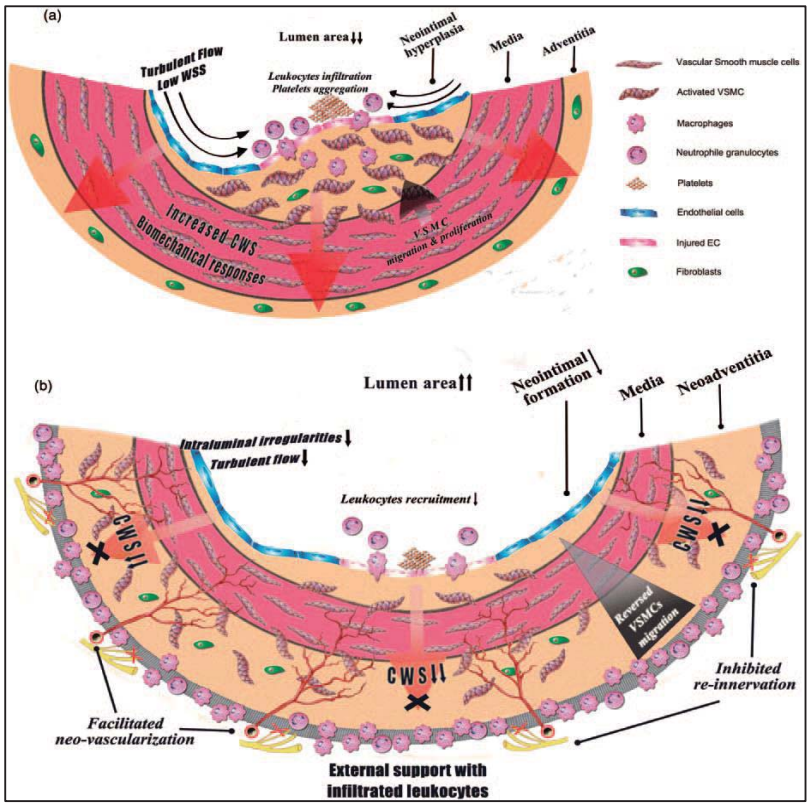

Figure 3: (Adapted from Hu & Wan (13)): Schematic diagram illustrating the pathogenesis of venous wall over-thickening and the mechanisms involved in external stenting of the vein graft: (a) failure of unsupported vein grafts due to neointimal hyperplasia and incorporated atherogenesis; (b) external prostheses preventing the venous wall from abrupt biomechanical changes through perivascular mechanical support, redirecting smooth muscle cell migration, facilitating neo-adventitial revascularization, and inhibiting re-innervation. CWS: circumferential wall stress; EC: endothelial cells; VSMC: vascular smooth muscle cells; WSS: wall shear stress

Table 1: Processes of intimal hyperplasia formation and the respective external support mechanisms of action

Intimal hyperplasia proliferation mode	External support potential inhibitory effect (13)
Wall stretch and activation of signaling molecules triggering proliferation and migration of smooth muscle cells.	An external support enables external reinforcement, limits abrupt dilatation and thus minimizes the wall stretch trigger
Remodeling of the vein graft directed at achieving arterial wall thickness to lumen radius ratio causes lumen irregularities.	An external support inhibits remodeling and promotes lumen uniformity
Turbulent and oscillatory flow caused by lumen irregularity adversely affects the blood-endothelial interface, activating smooth muscle cells and platelet aggregation.	An external support maintains lumen uniformity, hence inhibits turbulence and flow oscillations.
Dysfunction of vascular vasa-vasorum due to the harvesting procedure causes migration of smooth muscle cells and fibroblasts towards the inner layer, oxygenating by the oxygen rich arterial circulation.	An external support triggers growth of neo-adventitial vasculature which supplies the venous wall and inhibits inward migration of smooth muscle cells.
Inward migration of smooth muscle cells	An external support causes foreign body reaction which promotes outward redirection of the migration of smooth muscle cells and fibroblasts (accumulating around the external support) instead of migrating inwards.

2.3 The VEST

VEST (Venous External Support) manufactured by Vascular Graft Solutions Ltd, is an external mechanical support for autologous saphenous vein grafts that are created during Coronary Artery Bypass Surgery (CABG). The VEST (Figure 4, Figure 5) is deployed over the vein graft by the cardiac surgeon during the CABG procedure in a simple user-friendly manner. The implantation process takes only 1 minute and does not add any significant time to the overall CABG duration. The VEST does not require attachment to the vein graft or to the anastomoses by any external means (sutures or glue).

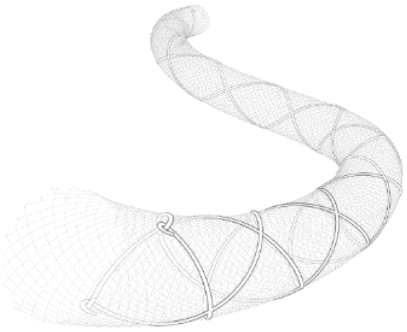

Figure 4: The VEST

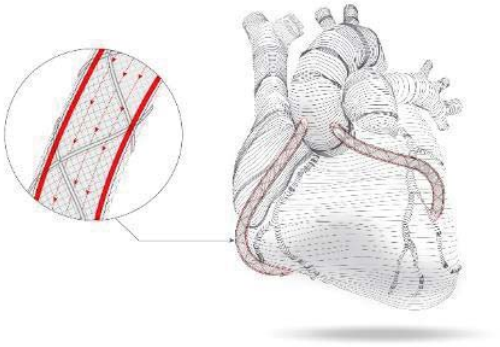

Figure 5: Two VESTs deployed over SVGs

The VEST is designed to target the underlying factors leading to SVG disease progression and, in particular, proliferation of intimal hyperplasia. Several effect modes are combined to deliver the desired effect:

- Prevention of post implantation dilatation
- Restraining wall tension
- Prevention of graft ectasia (segmental dilatation)
- Mitigation of occlusive thrombosis
- Enhancing diameter match with coronary artery
- Maintaining lumen uniformity
- Improving flow patterns

2.3.1. Intended Use

The VEST is indicated for use in limiting intimal hyperplasia by providing permanent support to saphenous vein grafts which are being used as conduits in patients who undergo coronary artery bypass grafting procedures as treatment for coronary arteriosclerotic disease. Information on product design and accessories is available in the device Instructions for Use.

3. Overall Study Design

3.1 Structure

This is a prospective, multi-center, randomized, within-subject-controlled trial, enrolling patients with multi vessel atherosclerotic coronary artery disease, scheduled to undergo SVG CABG with arterial grafting of IMA to LAD and two or more saphenous vein grafts. In each patient, one SVG bypass will be randomized to be supported by the VEST, while another will not be supported and serve as control. Thus, the full cohort will provide a basis for comparison of the primary endpoint between two sets of SVGs: A VEST-supported set; and a non-supported set. While the primary endpoint is assessed at 12 months post randomization, patient follow-up will continue for 5 years in order to demonstrate long-term outcomes of the VEST.

3.2 Rationale for Primary Endpoint

The primary endpoint is the degree of intimal hyperplasia at one year as assessed by IVUS. Missing IVUS data due to vessel occlusion will be imputed using a non-ignorable mechanism (not missing at random). The rationale for analyzing this endpoint in this manner is that it reflects efficacy in reducing intimal hyperplasia

and does not exclude occluded vessels, which are a safety concern. Proliferation of intimal hyperplasia is an ongoing process over years post CABG. The presumed efficacy of the VEST is its ability to slow down the rate of intimal hyperplasia formation. This study is designed to evaluate the difference between intimal hyperplasia area of VEST supported and unsupported vein grafts at one year after randomization. The within-subject design has advantages in that it reduces between-treatment variability by having each patient serve as their own control, but affects the ability to attribute serious adverse events to a treatment. We will capture serious adverse events in this trial, including MACCE.

3.3 Randomization

For every patient, a pair of grafts will be designated for participation in the trial; one to be supported with the VEST device and the other to serve as a control. Grafts to the LAD do not participate in the randomization.

Patients will be block randomized by territory and/or by SVG length.

If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will assign the treatment and control vessels by their lengths.

Only grafts originating proximally from the aorta will be considered for randomization. ***Sequential grafts will not be included in the study.*** Where more than one graft may be performed per territory, the vein grafts will be uniquely distinguished by their pre-measured length as "Longest" and "Shortest". This design will allow for within-subject comparisons, which is expected to increase power relative to a between-subject design.

To prevent any bias as well as exclude any ineligible patients, randomization will be performed only after the procedure has reached the stage where all venous bypass distal anastomoses have been constructed.

3.4 Masking

The nature of the study precludes masking surgeons from treatment assignment. In order to prevent selection bias, randomization into treatment assignment is performed intraoperatively only after all distal anastomoses have been completed (see section 6.2). Investigators will also be blinded to all data from other clinical sites, as well as the primary outcomes data and aggregate data regarding clinical outcome. Serious unexpected AEs will be reported to Institutional Review Board (IRB) as usual. Clinical events including serious and protocol-defined adverse events will be reviewed by an Event Adjudication Committee. All angiograms and intimal hyperplasia scoring will be analyzed, according to predefined analysis protocols, by independent core laboratory personnel who will be blinded to clinical outcomes.

4. Study Population

4.1 Number of Patients

A total of 224 subjects will be enrolled in up to 20 US and Canadian sites.

4.2 Eligibility Criteria

4.2.1. Inclusion Criteria

Eligible patients will meet all the following inclusion criteria:

1. Signed informed consent, inclusive of release of medical information, and Health Insurance Portability and Accountability Act (HIPAA) documentation.
2. Age 21 years or older.
3. Planned and scheduled on-pump CABG.
4. Two or more vein grafts to native vessels having at least 75% stenosis and comparable runoff.
5. IMA graft indicated for the LAD. Additional arterial grafts may be considered based on practice guidelines.
6. Appropriately sized and accessible target coronary arteries, with a minimum diameter of 1.5 mm and adequate vascular bed (without significant distal stenosis), as assessed by pre-operative cardiac angiography and verified by diameter gauging intraoperatively.

4.2.2. Exclusion Criteria

Patients will be excluded if they meet any of the following:

1. Concomitant non-CABG cardiac procedure.

2. Prior cardiac surgery.
3. Emergency CABG surgery.
4. Contraindication for on-pump CABG with cardioplegic arrest (e.g. severely calcified aorta).
5. Calcification at the intended anastomotic sites, as assessed upon opening of the chest and before randomization.
6. Severe vein varicosity as assessed after vein harvesting and before randomization.
7. History of clinical stroke within 3 months prior to randomization.
8. Severe renal dysfunction (Cr>2.0 mg/dL).
9. Documented or suspected untreated diffuse peripheral vascular disease such as: carotid stenosis or claudication of the extremities.
10. Concomitant life-threatening disease likely to limit life expectancy to less than two years.
11. Inability to tolerate or comply with required guideline-based post-operative drug regimen (antiplatelet plus statin) and/or inability to take aspirin.
12. Inability to comply with required follow-ups including angiographic imaging methods (e.g. contrast allergy).
13. Concurrent participation in an interventional (drug or device) trial.

4.3 Recruitment Strategies

CABG is a prevalent cardiac surgical procedure conducted within the participating Cardiothoracic Surgical Trials Network (CTSN) centers. We will establish enrollment targets for each clinical site based on a review of screening registration form. Enrollment strategies may include mailings to referring physicians of the study hospitals, symposia, and health care events targeted towards this population as well as telephone calls to neighboring health care facilities. The DCC will regularly assess actual enrollment in relation to pre-specified accrual goals, and additional interventions to facilitate enrollment will be implemented as needed. The Screening Registration form will identify numbers of patients screened and reasons for ineligibility and/or non-enrollment into the trial.

4.4 Inclusion of Women and Minorities

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

- Documentation of the number of women and minorities screened and enrolled via screening registration form;
- Monitoring of such logs from each clinical center on a regular basis;
- If necessary, develop and implement outreach programs designed to recruit adequate numbers of women or minorities.

4.5 Relevance to Medicare beneficiaries

The cohort eligible for participation in this study are all patients with multivessel coronary artery disease scheduled to undergo CABG procedure. From the literature (1,8) we know that CABG patients are typically with a median age of 64-65 years. Hence it is expected that approximately half the patients will be Medicare beneficiaries.

5. Definitions and Measurements of Endpoints and Outcomes

5.1 Primary Endpoint

The primary endpoint is defined as intimal hyperplasia (plaque+media) area [mm^2] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (VEST supported and unsupported) and is measured as a continuous variable.

5.2 Secondary Confirmatory Endpoints

1. *Lumen diameter uniformity* will be assessed by angiography for each graft separately and expressed by the Fitzgibbon classification (22), on a 3-point ordinal scale:
   - I – No intimal irregularity

- II – Irregularity of <50% of estimated intimal surface
- III – Irregularity of >50% of estimated intimal surface

2. *Graft Failure* coded as follows:
0 = Failure = ≥50% stenosis by QCA at 12 months
1 = Success = Otherwise

5.3 Additional Secondary Endpoints

- *Intimal hyperplasia:* (plaque + media) thickness [mm] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (supported and unsupported) and is measured as a continuous variable.
- *TIMI flow grade* assessed by angiography at 12 months on the following 4-point ordinal scale:
  - Grade 0 – No perfusion
  - Grade 1 – Penetration without perfusion
  - Grade 2 – Partial perfusion
  - Grade 3 – Complete perfusion
- *Graft failure* at 12 months, as defined above, separately for right and left territories
- *Repeat revascularization* for supported and unsupported vein grafts (or respective bypassed target coronary artery) over the 5 years of observation
- *Lumen diameter uniformity* expressed by the coefficient of variance (CV) by QCA at 12 months, computed for each graft separately and scored continuously as follows:

$CV_{Uniformity} = SD_{Diameter}/Mean_{Diameter}$

- *Ratio of vein graft lumen diameter to target artery lumen diameter* by QCA at 12 months

5.4 Clinical Events

- Mortality

All-cause mortality will be assessed.

- Hospitalizations
  - Length of Index Hospitalization

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

  - Readmissions

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

- Safety
  - Serious Adverse Events occurring post randomization and up to 12 months after the CABG procedure

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

- MACCE

Major adverse cardiac and cerebrovascular events (MACCE) occurring within 12 months and annually after up to 60 months after the index CABG procedure. MACCE is defined below.

  - All-cause **mortality**;
  - **Stroke** - Defined as any new, rapidly developing focal neurological deficit, lasting longer than 24 hours, ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests, imaging and neurology consultation note). The Modified Rankin Scale and the NIH Stroke Scale must be administered within 24 hours following the event to document the presence and severity of neurological deficits.
    Each neurological event must be subcategorized as:
    - Hemorrhagic stroke
    - Ischemic stroke
    - Other
  - **Myocardial infarction (MI)** – Any one of the following criteria meets the diagnosis of MI

- **Acute MI** - Detection of rise and/or fall of cardiac biomarker values (preferably troponin) with at least one value above the 99th percentile of the Upper Reference Limit (URL) and with at least one of the following:
  - Symptoms of ischemia;
  - New or presumably new significant ST-T changes or new LBBB;
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium, or new regional wall motion abnormality;
  - Identification of an intracoronary thrombus by angiography or autopsy
- **CABG related MI** - defined by elevation of cardiac biomarker values (>10 x 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either
  - New pathological Q waves or new LBBB, or
  - Angiographic documented new graft or new native coronary artery occlusion, or
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- **Prior MI** – Any one of the following criteria meets the diagnosis for prior MI:
  - Pathological Q waves with or without symptoms in the absence of non-ischemic causes
  - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence on non-ischemic cause.
  - Pathological finding of prior MI

- **Ischemic driven target vessel revascularization** - (CABG or PCI) of **VEST supported** vein graft or associated target coronary artery.
  Revascularization is considered ischemic driven if the subject has clinical or functional ischemia manifesting in any of the following:
  - **A history of angina pectoris** presumably related to the target vessel
  - **Objective signs of ischemia at rest** (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
  - **Abnormal results of any invasive functional diagnostic test** [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

  The angiography and IVUS procedure performed at 12 months to assess the graft integrity by the study plan will not be counted as MACCE. Clinical evaluation for the 12 months visit will be completed and MACCE will be recorded **prior to** performance of the planned interventional procedure. If revascularization of the VEST supported graft or associated bypassed coronary artery is performed as a result of the angiography, it will be reported and adjudicated according to the definition given above for ischemic driven target vessel revascularization, for assessment of MACCE at time points >12 months.

- COVID-19 – A diagnosis of coronavirus disease 2019 (COVID-19) confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay or other diagnostic test.
- *Time to revascularization* for supported and unsupported vein grafts (or respective bypassed target coronary artery). See above definition for revascularization.
- *Revascularization rate* for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years. See above definition for revascularization
- *Time to MI in culprit vessels*, for supported and unsupported vein grafts (or respective bypassed target coronary artery). See above definition for MI
- *Rate of MI in culprit vessels*, for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years. See above for definition of MI.

5.5 Anticipated Adverse Event Definitions and reporting rules

The following complications and adverse events are documented in the literature (5,8) and expected to occur with CABG patients. For the purposes of the trial, in line with IDE and Health Canada regulations, unanticipated adverse device effects (UADE) which are both serious and unexpected (not defined below) and meet the below definition, will be reported by sponsor to FDA/HC and reviewing IRB/REBs. Reports to Health Canada will include adverse device related incidents that occur in Canada that fit the criteria as specified in section 59 of the regulations.

Investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB/REB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, HC (even if anticipated) all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

Serious Adverse Event: Serious adverse events (SAEs) are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; results in a congenital anomaly/birth defect; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators or Sponsor. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

UADE is defined in CFR 812.3(s) as: "any serious adverse effect on 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.

Bleeding

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

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

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

Cardiac Arrhythmias

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

Cardiac arrhythmias are classified as follows:

- Cardiac arrest
- Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
- Cardiac conduction abnormalities or sustained bradycardia requiring permanent pacemaker placement (includes all PPMs whether associated with a serious AE or not)

Pericardial Fluid Collection

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

Pleural Effusion

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

Pneumothorax

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

Hepatic Dysfunction

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

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

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

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

Major Infection

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Localized Infection

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

Endocarditis

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

Sepsis

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

Sudden Unexpected Cardiac Death

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

Renal Failure

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

Respiratory Failure

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

Heart Failure

Signs of inadequate organ perfusion or congestion, or a syndrome of compromised exertional tolerance manifested by dyspnea or fatigue that requires

- intravenous therapy (diuretics, inotropic support, or vasodilators) and prolongs hospital stay in the judgment of the investigator, or
- introduction of intravenous therapy (diuretics, inotropic support, or vasodilators) at any point following discharge from the index hospitalization, or
- readmission for heart failure

Arterial Non-CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

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

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

Revascularization procedure
Revascularizations procedures which occur during the investigation must be reported to Sponsor as soon as possible. Every procedure will be recorded on a Revascularization CRF and the event documented as an adverse event on an Adverse Event CRF.

Other
An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

6. Data Collection Procedures

6.1 Screening and Baseline

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

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

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

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

Release of Medical Information Form
Prior to screening data collection and protocol defined procedures
The patient must sign the Release of Medical Information form or institutional equivalent that authorizes release of medical records, including hospital costing data, to the study Sponsor, investigators and monitors.

Medical History
Within 30 days prior to randomization
This form captures the information pertaining to the medical history including but not limited to previous myocardial infarction, myocardial revascularization, heart failure (NYHA, CCS classifications), stroke, and other comorbidities such as diabetes, hyperlipidemia, and peripheral vascular disease. Information regarding the current medical condition is also captured including but not limited to disposition at time of screening (outpatient, inpatient, ICU, etc.).

Laboratory Assessment
Within 30 days prior to randomization
Creatinine *(mg/dl)* value will be recorded as well as PTT and CK-MB.

Angiography
Within 6 months of randomization
Angiographic data must be available for every candidate patient to assess inclusion criteria. This form captures the date(s) of angiography and all coronary anatomy.

Medications
Within 30 days prior to randomization
This form captures all categories of medications (including but not limited to cardiovascular medications) at one pre-operative time point.

Physical Examination
Within 30 days prior to randomization
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Eligibility Criteria/Eligibility Evaluation Form
Prior to randomization
The inclusion and exclusion criteria will be reviewed and eligibility confirmed by the study team in the operating room just prior to randomization (see section 6.2). The Eligibility Evaluation Form must be completed by the clinical site study coordinator and verified within 48 hours of randomization with a signature and date by the investigator. All screened patients (patients who are consented) who are not randomized in the trial will have the reasons for non-randomization documented in the Eligibility Evaluation Form. The data collected are HIPAA compliant and include reason for not being randomized.

A representative from the DCC will be available to discuss any questions regarding patient eligibility.

6.2 Randomization

The randomization procedure will be performed inside the OR after confirmation by the surgical team of the patient's eligibility to randomize and performed only after the procedure has reached the stage where all distal anastomoses of the venous grafts have been constructed, to minimize bias and the chance of a randomized patient not participating in the trial. Randomization to the study assignment will be generated by the Electronic Data Capture (EDC) system once the checklist of inclusion and exclusion criteria has been completed and verified. For the purpose of the primary analysis, patients are considered enrolled in the study once they are randomized and an identification code is generated.

6.3 Treatment Interventions

All patients enrolled in this trial will undergo surgical CABG. For each patient, two SVG vessels will be assigned to either a VEST-supported or a non-VEST-supported (control) therapy.

All procedures will be performed using a median sternotomy incision, cardiopulmonary bypass support, and cardioplegic arrest. The management of cardiopulmonary bypass and myocardial protection will be at the discretion of the surgeon, using standard techniques.

Coronary Artery Bypass Grafting (CABG)
For the vein graft assigned to control, coronary artery bypass grafting will be performed using standard surgical techniques. Conduit selection and harvesting methods will not be prescribed, except that an IMA will be utilized when an LAD graft is indicated. The technical details of bypass grafting will not be prescribed. Complete revascularization will be performed, within the judgment of the surgical investigator.

Surgical Procedure
Initial surgical intervention
The initial surgical procedure (CABG) must be reported on the surgical procedure form within 48 hours of the event. Operative data such as cross-clamp time, additional procedures performed at the time of the operation, and intra-operative blood transfusions, will also be collected. Data should be collected including but not limited to: procedure details (all grafts performed, venous, arterial, target arteries, graft diameters and lengths, vein harvesting and preservation technique, origin above/below the knee, varicosity), VEST implantation procedure (graft length and diameter assessment, model selection, serial number, technical

success), randomization (time of all distal anastomoses completion, time of randomization, VEST supported graft, control graft), TTFM flow and pulsatility index measurements for all venous and arterial grafts.

6.3.1. Post-operative Medical Management

All patients will be prescribed statins and aspirin per practice guidelines (5) for 12 months. All other routine follow up will be performed in addition to study specifics detailed below.

6.4 Post-Randomization Data Collection

Study Visits

- Peri-operative
- Six weeks post-intervention *(± 2 weeks); Visit may be conducted remotely if the patient is unable to return to study site*
- Six months post-intervention *(± 30 days); Visit may be conducted remotely if the patient is unable to return to study site*
- 12 months post-intervention *(± 30days)* preceded by a phone call 6 weeks in advance
- Two, three, four, and five years post-intervention *(± 90 days); Visits may be conducted remotely if the patient is unable to return to study site*

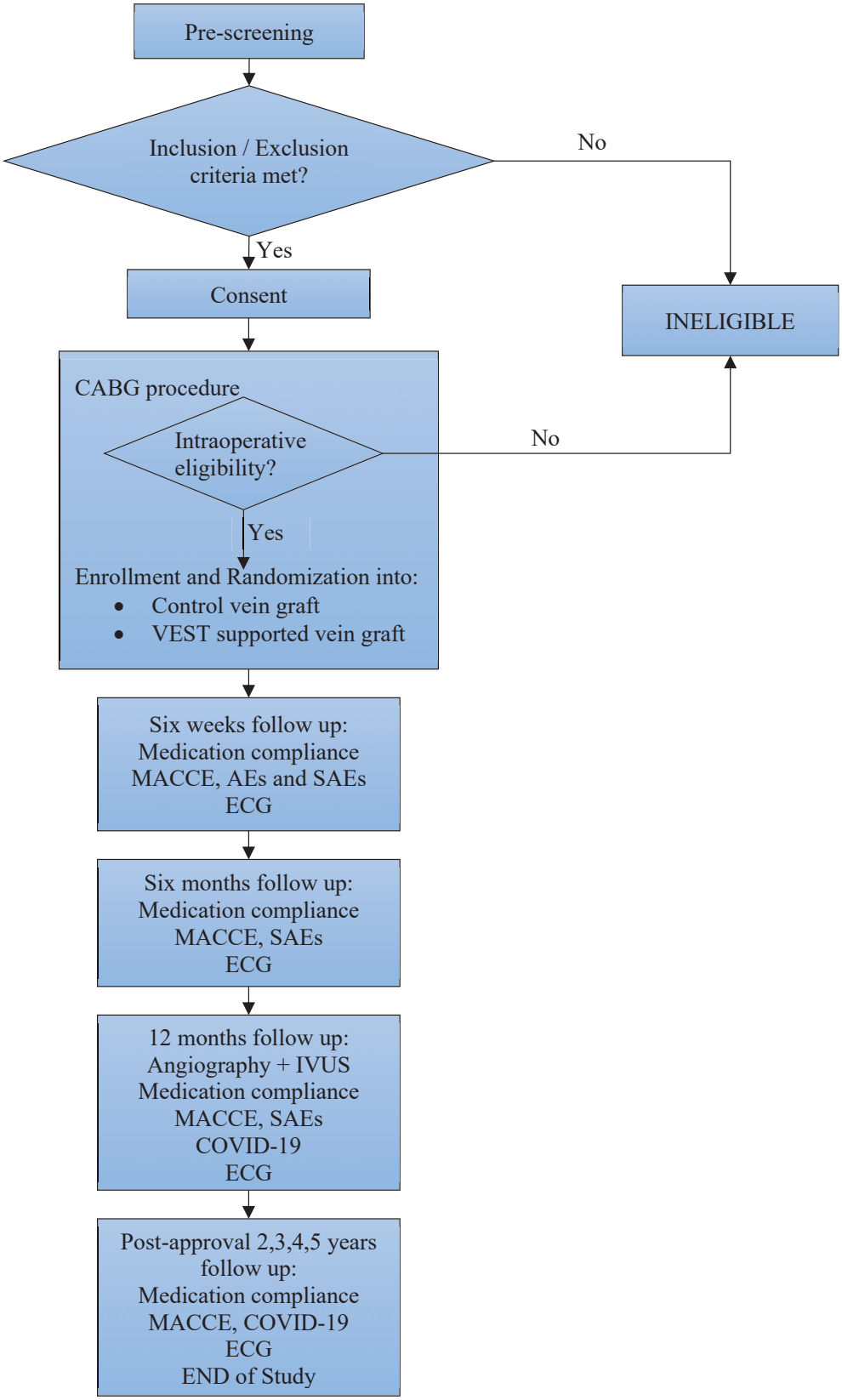

Figure 6: Study flow diagram

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

Medications
At 6 weeks (± 2 weeks), 6 months (± 30 days), 12 months (±30 days) and 2, 3, 4, 5 years (±90 days) post procedure and event-driven
All patients will be prescribed statins and aspirin per practice guidelines [5] for 12 months. These and all cardiovascular medications will be recorded at each study visit and also as indicated at the time of associated adverse events.

12 Lead ECG
At 6 weeks (± 2 weeks), 6 months (± 30 days), 12 months (±30 days) and 2, 3, 4, 5 years (±90 days) post procedure and event-driven
ECG results and interpretation will be collected.

Physical Examination
At 12 months (±30 days)
This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight).

Coronary angiography
At 12 months (±30 days)
Since this follow-up visit generates the primary endpoint data and completeness of data, each subject will be telephoned 6 weeks before the 1 year post-op date, to be reminded of the upcoming follow up visit and to schedule the appointment.

Coronary angiography – Contrast angiography will be attempted for all grafts and native vessels. Assessment of the patency/stenosis of the vein grafts and treated coronary arteries will be captured.

Coronary Angiography (QCA) by a core lab will be used to analyze data from patent grafts. Data will include Fitzgibbon classification I, II, III), percentage of vessel stenosis, ectatic lesions, blood flow, blood velocity, lumen diameters averaged over 1 mm intervals, TIMI flow grade, Syntax Score of native coronary vessels only.

Intravascular ultrasound (IVUS)
At 12 months (±30 days)
The IVUS catheter will be advanced all the way through each of two study vein grafts (providing patency has been demonstrated by contrast angiography) and pulled back (motorized) at a constant rate.
Images will be recorded and uploaded via the EDC for offline analysis by the independent IVUS core lab.

Event Driven Data Collection
Adverse Events
Event Driven
Detailed information regarding adverse events will be recorded at the time an adverse event becomes known. Relevant source documents and data will be collected including cost data pertaining to MACCE events. Investigators will be asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention. All serious adverse events will be recorded until the patient completes 12 months follow up. MACCE and diagnosis of COVID-19 will be collected throughout 60 months post randomization.

AEs are collected up to 6 weeks post procedure, SAEs are collected up to one year, MACCE and diagnosis of COVID-19 are collected for the duration of the study.

Common medical events (as determined by the investigator) such as colds, influenza, elective minor outpatient procedures such as colonoscopy, minor trauma and musculoskeletal discomforts do not need to be collected as adverse events unless they are serious, as defined in section 5.5. Events related to pre-existing

non-cardiac ailments such as arthritis, gout, gastrointestinal reflux disorder do not need to be collected as adverse events unless they are serious as defined in section 5.5.

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

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

Neurologic Dysfunction Assessment
Event Driven
The Modified Rankin Scale (Appendix I) and NIHSS (Appendix II) should be administered by a certified evaluator at the time of a cerebrovascular thromboembolic event (within 72 hours following the event) and at the termination of trial follow-up to document the presence and severity of neurological deficits.

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

Additional Procedures
Event driven
All procedures following the initial study defined surgical intervention must be reported on the surgical procedure form within 48 hours of the knowledge of the event. If the operation is to address a complication, the coordinator must also complete an adverse event report.

Collection of procedure data is in line with timelines defined for AE collection above: AEs are collected up to 6 weeks post procedure, SAEs are collected up to one year, and MACCE are collected for the duration of the study.

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

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

Patients reserve the right to withdraw from the study at any time without jeopardy to future medical care. All follow-up assessments and procedures should be performed and recorded up to the time of withdrawal. They may also be administratively withdrawn if they do not return for follow-up visits. If an AE is ongoing at the time of the withdrawal, the treating investigator will attempt to follow the patient until the AE has resolved or stabilized or until follow-up is no longer possible.

If the patient misses a scheduled study visit, the site will attempt to contact the patient to determine and document the reason the patient has failed to return, to obtain any information on medication, adverse events, and to encourage compliance with the study visit schedule.

Investigator's Statement
End of study

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

6.5 End Of Trial

The end of the pivotal trial will be declared when the last patient recruited completes the "12 months" visit. After study completion, patients will be followed by their respective doctors as per standard of care for patients in their condition. Follow-up will continue in the post-approval phase until the last patient reaches 5 year follow-up, as noted above.

6.5.1. Compliance with Protocol

The site Principal Investigator is considered responsible for compliance with the protocol at the investigational site. The Principal Investigator is also responsible for reporting all protocol deviations to the respective IRB and to the DCC. A representative of the DCC will make frequent contact with the Principal Investigator and his/her research staff and will conduct regular monitoring visits at the site to review patient data and device accountability records for compliance with the protocol, e.g., patient eligibility criteria, randomization assignments, device model selection, procedures performed, and follow-up visit schedule.

7. Risk-Benefit Considerations

In all clinical use to date (over 500 patients) the VEST has not been associated with any device related adverse events. The potential benefits of the VEST are in mitigation of vein graft disease parameters such as intimal hyperplasia, lumen non-uniformity and disturbed flow patterns. This potential effect has been observed over a follow up duration of 1 year in a 30 patient pilot study performed in the UK.

The VEST should be implanted by trained professional cardiac surgeons. Care should be taken to use the VEST according to the IFU. The VEST model should be carefully selected according to instructions for use. There is some risk of VEST interfering with side branch ligations or masking kinks in the vein graft, however this can be mitigated with training and careful attention to instructions. Once deployed and expanded on the vein graft, the VEST can, at any time, be recompressed, for inspection and correction of the vein graft, and subsequently re-expanded.

Potentially, if incorrectly placed, the VEST can lead to vein graft failure which in turn can lead to MI or need for additional intervention. This risk can be significantly mitigated by careful model selection, avoidance of metal clips, avoidance of interference with the anastomoses, and careful compliance with the IFU.

Additional potential adverse effects associated with the VEST may include the complications reported for conventional coronary artery bypass grafting procedure such as: vein graft failure, MI, stroke, ventricular fibrillation, impaired cardiac rhythm, infection, bleeding, death, or need for repeat revascularization.

In summary, while the potential benefits in mitigating vein graft disease are promising, the risks are mainly due to those associated with any CABG surgery and the adjunct use of the VEST ads minimal risk which can be mitigated with careful training and compliance with IFU.

Other risks associated with coronary artery disease and/or major surgery, such as CABG, apply to these patients, but are not expected to be influenced by use of the VEST.

8. Statistical Considerations

8.1 General Design Issues

This study is a prospective, multi-center, randomized clinical trial that will enroll patients with multi-vessel disease undergoing CABG. The novel VEST treatment will be randomly assigned with equal probability to either a right or left and/or short or long vein graft within each patient. The nature of the treatments precludes masking of treating clinicians to treatment assignment; however, investigators will be masked to data from other clinical sites with the exception of reportable UADE: serious, unanticipated device related or possibly related AEs, which must be revealed for IRB/REB -reporting purposes. The trial’s primary aim is to determine whether the VEST device is safe and effective for its intended use in supporting saphenous vein grafts used as conduits in patients who undergo CABG for coronary arteriosclerotic disease.

The within-patient design takes advantage of the positive correlation between intimal hyperplasia (IH) measured on grafts within the same patient, to produce a less variable measure of treatment difference, and so increase power compared to between-patient designs.

8.2 Analysis Sets

8.2.1. Safety Analysis Set

The safety analysis set will consist of all patients who are considered enrolled in the study, once they are randomized and an identification code is generated.

Handling of missing data: Only observed values will be used to analyze safety data; i.e. missing safety data will not be imputed.

8.2.2. Full Analysis Set

The full analysis set (FAS) will, consistent with ICH Guideline E9 (35), include all randomized vessels for whom the study procedure was initiated in either arm according to the intent-to-treat (ITT) principle.

8.3 Sample Size Justification

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for patients undergoing CABG. The primary endpoint of the study will be the intimal hyperplasia (plaque + media) area [mm^2] as assessed by IVUS at 12 months post randomization. Sample size is based on the assumption that IH will be normally distributed with standard deviation of 1.7 mm^2 in both the VEST supported and the unsupported vessels. We also assume that the mean IH in the unsupported vessel is 5.1 mm^2 and that the correlation between IH measured on grafts within the same patient is equal to 0.5. In addition, we anticipate that approximately 13% of patients will have the supported and/or unsupported grafts occluded or severely stenosed and so unable to have IH measured through IVUS; in approximately 50% of these patients IH will not be obtained in either graft, while in the rest, the occlusion will only affect one of the two graft, in 25% the VEST graft will be occluded and in 25% the control graft will be occluded). Although it is unclear to what extent occlusion is related to IH one year post CABG, we will treat missing values of IH resulting from occluded vessels as non-ignorable missing (see below section) using an imputation model that will penalize these vessels and will reduce the effect size. Therefore, we assume a conservative effect size of 0.4 mm^2, or a reduction of IH in the VEST vessels compared to the control vessel of about 8%.

Under these assumptions, fixing the power at 90% we need to enroll 190 patients, before adjustment for loss to follow-up.

Lost to follow up and refusals: The term “lost to follow-up” is used to describe an individual who has withdrawn consent to be in the study or who can no longer be located or assessed. Such individuals represent those for whom primary outcome assessment is no longer possible. We anticipate that the loss to follow-up rate or refusal to perform an IVUS in this study will be around 15%. To account for this loss to follow up rate a total of 224 eligible participants will be enrolled in the study.

8.4 Randomization Design and Procedure

Randomization will be performed only after the procedure has reached the stage where all distal anastomoses of venous grafts have been constructed. Subjects will be block randomized by territory and/or by SVG length.

If vein grafts are performed to both the right and the left territories, randomization will assign either the right or the left grafts to receive the VEST device. If there are two or more vein grafts per territory, randomization will assign the treatment and control vessel by their lengths.

Only grafts originating proximally from the aorta will be considered for randomization. Sequential grafts will not be included in the study. Where more than one graft may be performed per territory, the vein grafts will be uniquely distinguished by their pre-measured length as “Longest” and “Shortest”.

8.5 Statistical Analysis

8.5.1. Overview

Data will be summarized in tables using descriptive statistics (mean, standard deviation, median, minimum, maximum and number of subjects) for continuous data, or in frequency tables for categorical data. Tables will be presented by study arm and overall. Data listing by subject will be provided.

8.5.2. Subject Disposition

Subject disposition will be tabulated; the number of enrolled, exposed, prematurely terminated and completed subjects will be summarized, including the number of subjects in each analysis population.

A list of dropouts will be prepared including reason for discontinuation, and time of discontinuation.

8.6 Analysis of the primary endpoint

The primary outcome is the degree of intimal hyperplasia at 12 months post-surgical intervention, assessed by IVUS. The null hypothesis is that there is no difference in the 12-month intimal hyperplasia between vessels randomized to the VEST compared to control vessels. The primary null hypothesis will be tested in an intent-to-treat analysis using a two-tailed 0.05 alpha level. The analysis will be conducted using a Wilcoxon signed-rank test. A multiple imputation approach will be used to impute the intimal hyperplasia values of the occluded vessels as described below. In addition, we will also account for the occluded vessels in the computation of the Wilcoxon signed-rank test as follows. If two vessels in the same individual are both occluded, we will assign an absolute value of zero for the difference between the two scores irrespective of the imputed values. Pairs with a value of zero will be excluded from the computation of the test statistic as usual for the Wilcoxon signed-rank test. If only one of the two vessels is occluded in the same individual, then we will assign an absolute value equal to the difference between the observed and the imputed score. The sign associated with the rank for this difference, however, will be in favor of the non-occluded vessel. If both vessels are not occluded they will be treated as usual in the computation of the Wilcoxon signed-rank test.

We anticipate that roughly 13% of vessels will be obstructed and unsuitable for IVUS, and thus intimal hyperplasia will be measured only on non-obstructed vessels. Although the degree of intimal hyperplasia may be independent of the mechanism of obstruction, we will consider an obstructed vessel as a failed vessel in the analysis. Specifically, we will assume a non-ignorable mechanism (not missing at random or NMAR) for the data missing due to obstructed vessels.

We will address the problem of missing IVUS data by multiple imputation — i.e., creating several potential imputed observations for each missing data using a predictive modeling (36). The underlying model will use the pattern-mixture approach, which posits a separate distribution of the true IVUS measurement for missing and non-missing observations. The model will include the following subject specific covariates: hypertension, diabetes, hyperlipidemia, and smoking status; and the following vessel specific covariates: treatment assignment, coronary territory, vein harvest and preservation techniques.

Let Y represent the continuous outcome variable (i.e. intimal hyperplasia) and let R be an indicator variable that assumes different values according to whether Y is observed or missing. Under a pattern-mixture model, the joint distribution of the outcome Y and the missing indicator variable R, $f(Y,R)$, is factorized into the density of the outcome, conditional on the pattern of missingness of Y, $f(Y|R)$, and the marginal distribution of the missing indicator variable, $P(R)$.

$$f(Y,R)=f(Y|R)P(R)$$

In longitudinal studies, the probability distribution $P(R)$ refers to the probabilities of the different possible patterns of missingness. In this situation we distinguish only two patterns of missing data: we define a case to be complete $(R=1)$ if a vessel is able to be evaluated at follow-up, and to be incomplete $(R=0)$ if the follow-up measurement is missing due to occlusion.

Under the NMAR framework, the density $f(Y|R)$ is specified differently depending on whether $R=0$ (Y is missing) or $R=1$ (Y is observed), reflecting the fact that the missing values may come from a different distribution than the observed ones. In this study, we will assume that the distribution function of intimal hyperplasia is normal, with $f(Y|R=1)\sim N(\mu, \sigma^2)$ for the observed data and $f(Y|R=0)\sim N(\mu+\delta, \gamma\sigma^2)$ for the missing data. The parameters δ and γ are sensitivity parameters. In order to "penalize" the obstructed vessels we will assume that δ is positive to reflect, on average, larger values of intimal hyperplasia. For the primary analysis, we will assume that the standard deviations of intimal hyperplasia for observed and missing data are the same ($\gamma=1$). In addition, we will assume that the non-observed values come from a normal distribution with mean $(\mu + \delta)$ equal to the 90th percentile of the distribution of intimal hyperplasia.

The parameter δ will be specified using data from the VEST I and the VEST III studies and determined as follows:

- In the VEST I trial the 90th percentile of the distribution of IH was 6.84 mm^2 and the aggregate mean was 4.77 mm^2, resulting in δ = 2.07 (6.84 -4.77; n=43).

- In the VEST III trial the 90th percentile for the IH distribution was 4.99 mm^2 and the aggregate mean was 3.48 mm^2, resulting in $\delta = 1.51$ (4.99 - 3.48; n=93).

The parameter δ is determined as the weighted average (based on number of vessels) of the δ from the two VEST studies, which is 1.70 mm^2. A simple simulation of 100000 random draws from a normal distribution with mean=1.70 and standard deviation=0.25 showed a minimum value of 0.60 and maximum value of 2.69. These values provide a reasonable range for which intimal hyperplasia can be shifted to higher values for missing data due to occlusion.

The procedure will be implemented in two stages: First we will create of a set of imputations for intimal hyperplasia for each patient with missing data due to an occluded vessel. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data. Characteristics of the vessels, like laterality and length as well as patients' characteristics will be used to inform the predictive models. This corresponds to the usual imputation under a missing at random (MAR) mechanism. In the second stage, values will be generated from a prior distribution $N(\delta, \sigma_\delta^2)$, where $\delta = 1.70$ mm^2 and $\sigma_\delta^2 = 0.25^2$, and added to the imputed response from the first stage for occluded vessels.

We will repeat the imputation process 30 times to achieve maximal stability of the procedure. A separate analysis will be conducted for each completed-and-imputed dataset. Rubin's rule (36) will be used to combine the 30 analyses and test the difference between intimal hyperplasia of the treated and control vessels.

For simplicity our primary analysis will not be stratified by clinical center, although the randomization will stratify by clinical center. This should result in only a small loss of efficiency.

Sensitivity Analysis

We will conduct a series of sensitivity analyses to determine the stability of the estimate of the treatment effect obtained with the multiple imputation pattern-mixture approach. Specifically, we will work with different values of the sensitivity parameter δ and γ to determine how our assumptions about the distribution of the missing data influence the results. For example, assuming $\delta = 0$ corresponds to a missing-at-random (MAR) assumption, which posits that there is no information in the fact that a vessel is occluded and therefore cannot be measured. These analyses will allow us to determine how large δ has to be to change the outcome of the final analysis with respect to statistical significance of the treatment effect.

Crossovers

Vessels randomized to VEST but not supported will be considered crossovers. Similarly, vessels randomized as control but VEST supported will be considered crossovers. We anticipate very few crossovers in this trial. As the primary analysis is by intention to treat, crossovers will be analyzed as belonging to the group to which they were randomized. The pattern of crossovers will be examined, and if differential crossover rates between arms are noted, further analyses will be performed to determine the effect of on trial outcomes.

Missing Data due to Missed Visits

Patients will be scheduled for a 12-month IVUS study, and patients should be carefully screened prior to randomization regarding their willingness to undergo an IVUS study. Despite this screening and ongoing communication with patients regarding the importance of study endpoint assessment, we anticipate that there will be 10-15% missing primary endpoint assessments. Patients missing primary endpoint assessments due to loss to follow-up are accounted for in the sample size calculation.

8.7 Analysis of Secondary Confirmatory Endpoints

Following are the study's two secondary confirmatory hypotheses that will be tested in the order presented using a sequential strategy:

Secondary Confirmatory I

H_0: $OR(\text{Fitzgibbon classification})_{\text{VEST vs. SOC}} = 1$
H_1: $OR(\text{Fitzgibbon classification})_{\text{VEST vs. SOC}} \neq 1$

Where $OR(\text{Fitzgibbon classification})_{\text{VEST vs. SOC}}$ represents the odds ratio (OR; VEST vs. SOC) for getting lower Fitzgibbon classification. Lumen diameter is measured using Fitzgibbon classification (scale of 1 to 3) as described in Section 5.2.
Hypotheses will be tested using a proportional odds model for clustered data with two-sided Alpha = 0.05. We will declare success on this endpoint if we will have succeeded on the primary efficacy endpoint and

rejected the null hypothesis in this section as a result of higher odds for getting lower Fitzgibbon classification for VEST compared to SOC.

Secondary Confirmatory II

H_0: $P(\text{Graft Failure})_{VEST} = P(\text{Graft Failure})_{SOC}$
H_1: $P(\text{Graft Failure})_{VEST} \neq P(\text{Graft Failure})_{SOC}$

Where $P(\text{Graft Failure})_{VEST}$ and $P(\text{Graft Failure})_{SOC}$ represent the proportion of graft failure in the VEST and control groups. Graft failure ("yes" or "no") is determined as described in Section 5.2.
Hypotheses will be tested using McNemar's test for paired binary observations with two-sided alpha = 0.05. We will declare success on this endpoint if we will have succeeded on both confirmatory endpoints.

8.8 Analysis of Additional Secondary Endpoints

The following additional secondary endpoints will be analyzed:

Intimal hyperplasia: (plaque + media) thickness [mm] as assessed by IVUS at 12 months. This endpoint is measured for each study graft (supported and unsupported) and is measured as a continuous variable. This secondary endpoint will be analyzed using mixed models with patients as random effects.

TIMI flow grade assessed by angiography at 12 months on the following 4-point ordinal scale:

- Grade 0 – No perfusion
- Grade 1 – Penetration without perfusion
- Grade 2 – Partial perfusion
- Grade 3 – Complete perfusion

This secondary endpoint will be analyzed using a Wilcoxon signed-rank test.

Graft failure at 12 months, as defined above, separately for right and left territories. This endpoint will be analyzed using McNemar's test for binary observations.

Repeat revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery) over the 5 years of observation. This endpoint will be analyzed using McNemar's Test for paired 2 x 2 tables.

Lumen diameter uniformity expressed by the coefficient of variance (CV) by QCA at 12 months, computed for each graft separately and scored continuously as follows:

$CV_{Uniformity} = SD_{Diameter}/Mean_{Diameter}$

Ratio of vein graft lumen diameter to target artery lumen diameter by QCA at 12 months.
The latter two endpoints will be analyzed using mixed-effect models with patient as random intercept.

8.9 Clinical Events

The clinical events will be tabulated and characterized using descriptive statistics. Time to death will be described using a Kaplan-Meier curves, adverse events (including MACCE) will be described as rates and proportions. 95% confidence intervals will be constructed around the point estimates.

8.10 Interim Analysis

There is no planned interim analysis.

8.11 Five-year Follow-up

Patients participating in this trial will be followed for an additional 4 years after completing the 12-month pivotal trial to assess the following endpoints:

- Revascularization rate for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years.
- Rate of MI culprit vessels, for supported and unsupported vein grafts (or respective bypassed target coronary artery) at 3 years, and at 5 years.
- Time to revascularization for supported and unsupported vein grafts (or respective bypassed target coronary artery).

- Time to MI in culprit vessels, for supported and unsupported vein grafts (or respective bypassed target coronary artery).

Rates at 3 and 5 years will be analyzed by McNemar's test if there are no recurrent events; otherwise Poisson regression will be used with robust standard errors. Time-to-event endpoints will be described using Kaplan-Meier curves and analyzed using the Cox Proportional hazards model with robust standard errors—with and without adjustment for individual covariates. While these analyses are pre-specified in the protocol, this study is not powered for these endpoints.

9. Data Collection, Study Monitoring, and Data Disclosure

9.1 Data Management

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

Quality Assurance

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

Additional external cross-form checks for data consistency and validation will be made by the DCC's data management team. Data will be monitored remotely at the DCC on an ongoing basis to check for inconsistencies in information across forms and for data outliers (typically values that fall in the highest or lowest 10% of the accumulated data and/or values that are outside the range of what is typically considered to be physiologically possible). Monitors will enter these queries through the EDC system for site coordinators to either correct or verify.

9.2 Study Monitoring and Source Data Verification

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

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

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

The monitors will review the source documents to determine whether the data reported in the EDC system are complete and accurate. They will also verify that all adverse events exist on the source documents, are consistent with the protocol, and are documented in the appropriate format. Source documents include medical charts, initial hospital admission reports, operative procedure records, discharge and re-admission

reports, consult notes, radiology reports, lab reports, clinic records, and other study-related notes. The study monitors reserve the right to copy de-identified records in support of all adverse events and outcomes.

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

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

If problems are identified during the monitoring visit (e.g., poor communication with the DCC, inadequate or insufficient staff to conduct the study, missing study documents, etc.), the monitor will assist the site in resolving the issues. Some issues may require input from the Steering Committee or the PI as well as the Sponsor.
Given the combination of approximately yearly on-site monitoring and ongoing monitoring using the EDC system that includes instantaneous electronic validation and visual cross-validation to detect complex errors, it is anticipated that the best possible quality and most complete data will be collected.

10. Organization of the Study

This section describes the overall study organization. The study is conducted in the clinical centers who participate in the Cardiothoracic Surgical Trials Network (CTSN). The trial is sponsored by VGS. The following committees and institutions will be involved in the administration of the study.

10.1 Event Adjudication Committee (EAC)

The charge of the Event Adjudication Committee (EAC) is to review source documents and adjudicate all serious adverse events and causes of mortality. The individuals who will serve on the committee have no formal involvement or conflict of interest with the clinical trial or the DCC, and will be appointed by the DCC. The committee will consist, at least, of a cardiothoracic surgeon, a cardiologist, and a neurologist. The EAC will meet 8 times annually or as needed to review outcomes data for each subject enrolled.

10.2 Data and Safety Monitoring Board (DSMB)

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor results during the study. The board consists of physicians, biostatisticians, ethicists, neurologists and bioengineers who have no formal involvement or conflict of interest with the subjects, the investigators, the DCC, or the clinical sites. The DSMB will act in a senior advisory capacity to the DCC and VGS regarding data and safety matters throughout the duration of the study. In addition, the DSMB will review interim summary results of the accumulating data from the Event Adjudication Committee every 6 months. These data include adverse events and mortality. They will communicate their findings directly with the DCC. The clinical centers will have no contact with the members of DSMB and no voting member of the committee may participate in the study as an investigator.

10.3 Clinical and Data Coordinating Center (DCC)

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

10.4 IVUS/Coronary Angiography Core Lab

The Coronary Angiography Core Lab, Mount Sinai Intravascular Imaging Core Laboratory of Icahn School of Medicine at Mount Sinai (1450 Madison Ave, New York, NY), is directed by Dr. Jagat Narula. All angiograms and intravascular ultrasounds will be performed according to a standardized protocol (see Manual of Operations) and will be centrally analyzed.

10.5 Site Qualification

The study will be conducted in up to 20 clinical centers participating in the Cardiothoracic Surgical Trials Network (CTSN). Each clinical center will be required to obtain IRB approval for the protocol and consent (and their revisions) in a timely fashion, to recruit patients, to collect data and enter it accurately in the electronic data capture (EDC) system, to faithfully follow the protocol and adhere to the standards of Good Clinical Practice (GCP). In addition, centers will be required to provide the Data Coordinating Center and Sponsor with the information necessary for interim, annual, and final reports, to provide source documents, data and regulatory documents for study monitors, provide prompt responses to DCC inquiries, and to participate in analyses and reporting of study results.

Investigator Profile

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

Qualifications and Training

Clinical investigators will be cardiothoracic surgeons with expertise in CABG. To qualify as a surgeon participating in this trial, the surgical investigator must have performed at least 20 on pump CABG procedures annually averaged over two years as an attending surgeon.

Cardiology investigators will have expertise in diagnostic angiography and IVUS and must have performed at least 10 procedures annually averaged over two years as an attending cardiologist.

Surgical physicians' assistants (PA) or nurse practitioners (NP) must have performed at least 20 vein graft harvest procedures annually averaged over two years since licensure.

Surgeon and cardiologist training for VEST

The surgical investigator, PA and/or NP will receive onsite training from the VGS representative. All cardiology investigators will receive an acquisition protocol for the angiography and IVUS.

All clinical site investigators and coordinators will be trained by the DCC in the specifics of the protocol during site initiation in advance of patient enrollment. In addition, the investigators and coordinators will undergo a separate training session to gain familiarity with the electronic data capture system.

Delegation of Authority and PI Oversight

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

Conflict of Interest and Financial Disclosure Agreement

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

Site Approval

The following documents must be collected prior to site approval and opening to patient enrollment:

- FDA IDE approval
- Signed Clinical Study Agreement with Vascular Graft Solutions, Ltd.
- Signed investigator agreement as approved in IDE G150225
- Signed Conflict of Interest Statements
- Completed Delegation of Authority Log
- Signed and dated CVs for all staff on Delegation of Authority Log

- Privacy training (HIPAA) and Human Subjects training documentation (as required by local institutional guidelines) for all staff on Delegation of Authority Log
- Current licenses for all staff on Delegation of Authority Log
- NIH Stroke Scale and Modified Rankin Scale Training Certification for delegated staff
- IRB roster
- IRB approval for protocol, informed consent document, HIPAA authorization
- Clinical Center Laboratory Certification
- Laboratory Normal Ranges
- Surgical Certification forms for Surgeons
- Cardiology Certification for Cardiologist
- NP/PA Certification forms
- Surgeon, NP/PA VEST training documents
- Signed Document Approval Form for protocol
- Study-specific training documents

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

10.6 Patient Confidentiality

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

10.7 Publications

The Sponsor and CTSN investigators plan to publish the outcomes of this study. Publication in writing and/or orally will take place after completion of the 1 year data collection and analysis or sooner if the study is terminated. Publication arrangements are detailed in the CTA.

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12. APPENDIX I: MODIFIED RANKIN SCALE (MRS)

Instructions: Assessment should be completed by a certified evaluator.

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

☐	0=	No symptoms at all
☐	1=	No significant disability, despite symptoms; able to carry out all usual duties and activities
☐	2=	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
☐	3=	Moderate disability; requiring some help, but able to walk without assistance
☐	4=	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
☐	5=	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

13. APPENDIX II: NIH STROKE SCALE (NIHSS)

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

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

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

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

1. Level of Consciousness

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

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

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

1c. LOC Commands
Say to the patient "open your eyes...now close your eyes" and then "Make a fist...now open your hand". Use the non-paretic limb. If amputation or other physical impediment prevents the response, use another suitable one step command. The priming phrase is not scored, and these are used only to set the eyes or hand in a testable position. That is, the patient may be asked first to open the eyes if they are closed when you begin the test. Scoring is done on the second phrase "close your eyes". Count the number of incorrect responses and give credit if an unequivocal attempt is made to perform the operative task, but is not completed due to weakness, pain or other obstruction. Only the first attempt is scored and the questions should be asked only once.

2. Gaze

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

3. Visual Fields

Visual fields are tested exactly as demonstrated in the training video. Use finger counting or movement to confrontation and evaluate upper and lower quadrants separately. A score of 3 is reserved for blindness from

any cause, including cortical blindness. A score of 2 is reserved for a complete hemianopia, and any partial visual field defect, including quadrant anopia, scores a 1.

4. Facial Movement (Facial Paresis)

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

5. Motor Arm-Right

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

Motor Arm-Left

See explanation of 5.

6. Motor Leg-Right

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

Motor Leg-Left

See explanation of 6.

7. Limb ataxia

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

Please indicate presence of ataxia in arms and legs.

8. Sensory

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

9. Best Language

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

10. Dysarthria

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

11. Extinction and Inattention (formerly Neglect)

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

Total Score: Please provide the total score for the subject as determined by the 11 categories of questions. Do not include scores of "9" in total.