VA Maryland Healthcare System

Cooperative Study CSP #588

Randomized Endo-Vein Graft Prospective (REGROUP) Trial

Statistical Analysis Plan

Version Number 3
August 30, 2018

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STATISTICAL ANALYSIS APPROVAL

Version 3.0

Responsibility	Name	Signature	Date
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1 INTRODUCTION

1.1 Preface

Coronary artery bypass grafting (CABG) is the most common major surgical procedure in the United States with over 300,000 cases performed each year. To restore blood flow to the heart, vascular conduits from another part of the body are procured to create a bypass around critically blocked coronary arteries. The left internal thoracic artery is the conduit of choice for CABG due to its superior long-term patency. However, almost all patients referred for CABG require additional grafts to provide complete revascularization. This necessitates the harvest of other vessels, most commonly the saphenous vein which is used almost ubiquitously in contemporary CABG with an average of two vein grafts per CABG procedure. In the last 10 years, endoscopic vein harvesting (EVH) has been recommended as the preferred method over the traditional open harvesting technique (OVH) for saphenous vein graft (SVG) harvesting because it provides a minimally invasive approach. However, more recent investigations indicate potential for reduced long-term bypass graft patency and worse clinical outcomes with EVH. The long-term impact of EVH on clinical outcomes has never been investigated on a large scale using a definitive, adequately powered, prospective Randomized Clinical Trial (RCT) with long-term follow-up. Results of the proposed study will fill a significant gap in existing knowledge regarding long-term outcomes for EVH in CABG, improving the quality of the care we provide to Veterans and more broadly to all patients undergoing coronary revascularization. Findings from this study have the potential to significantly impact the VA and national cardiac surgery coronary revascularization guidelines.

1.2 Goal of the analyses

The goal is to investigate the impact of SVG harvesting technique (OVH vs. EVH) on MACE (major adverse cardiac events), a composite end point of all-cause mortality, nonfatal myocardial infarction and repeat revascularization, leg wound complication, patient satisfaction, and quality of life in addition to determining the role of vein harvester's experience on clinical outcomes.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives and Hypotheses

Primary Objectives:

Objective 1: To investigate the impact of SVG harvesting techniques – OVH vs. EVH on MACE, a composite end point of all-cause mortality, nonfatal myocardial infarction and repeat revascularization, over the active follow-up period of the study postoperatively.

Hypothesis 1: A significantly smaller proportion of CABG subjects with SVGs harvested by open technique will experience MACE post-surgery compared to CABG subjects with SVGs harvested by endoscopic technique during the active follow-up period.

Secondary Objectives:

Objective 2: To investigate the impact of SVG harvesting techniques – OVH vs. EVH on MACE, a composite endpoint of all-cause mortality, nonfatal myocardial infarction and repeat revascularization, at one and three-year postoperatively.

Hypothesis 2: One-year composite MACE rate will be 6 percentage points lower in the open harvesting group and three-year composite MACE rates will be at least 8-10 percentage points lower in the open vein harvesting group compared to the endoscopic vein harvesting group.

Objective 3: To investigate the impact of SVG harvesting techniques – OVH vs. EVH on MACE, a composite endpoint of all-cause mortality, nonfatal myocardial infarction and repeat revascularization, over the entire follow-up period (active and passive) of the study postoperatively.

Hypothesis 3: A significant smaller proportion of CABG subjects with SVGs harvested by open technique will experience MACE post-surgery compared to CABG subjects with SVGs harvested by endoscopic technique during the entire follow-up period.

Tertiary Objectives:

Objective 4: Investigate the impact of the two harvesting techniques - open vs. endoscopic - on clinical indicators of leg wound complications and subject satisfaction at six weeks post-surgery.

Hypothesis 4: Leg wound complications will be lower and satisfaction will be higher in the EVH group compared to OVH group.

Objective 5: Compare subject quality of life scores according to the SVG harvest technique at six weeks post-surgery.

Hypothesis 5: Subjects' quality of life scores will be higher in the EVH group compared to the OVH group.

Objective 6: Determine the role of vein harvester experience on clinical outcomes.

Exploratory Aim with no hypothesis specified.

2.2 Endpoints

2.2.1 Primary Outcome Measures

The primary outcome measure is MACE following randomization and the index CABG.

For hypothesis 1: The outcome measure, MACE (major adverse cardiac events) is a composite endpoint that includes death (all-cause), myocardial infarction (MI), and revascularization for myocardial ischemia. Each randomized participant (either in EVH or OVH) will be followed after the index CABG to capture the time-to-MACE event where an 'EVENT' will be defined as either death (all-cause) or an MI or a revascularization procedure during the follow-up period. Total follow-up period will be 6.5 years of which the first 4.5 years will be active follow-up (using in-clinic visit or by telephone) period and will be carried out by the site personnel. The remaining 2 years will be passive follow-up which will be carried out centrally by the chair's office staff using VA clinical and administrative databases (CPRS, VASQIP, etc.). A minimum of 1 year of active follow-up will be used for participants who will be randomized at the tail end of the 3-year projected enrollment period of the study. The participants who will either be lost to follow-up or will not experience an 'EVENT' before the end of the follow-up period will be considered as right-censored. The primary analysis of such time-to-Mace event data will include the events only from the active follow-up period (which is approximately 4.5 years).

2.2.2 Secondary and Tertiary Outcome Measures

Secondary outcomes include MACE at one and three-year and over the entire follow-up period (active and passive) of the study postoperatively. Tertiary outcomes include leg wound complication and quality of life.

For hypothesis 2: MACE at one and three-year postoperatively.

For hypothesis 3: MACE over the entire follow-up period (active and passive) of the study postoperatively.

For hypothesis 4: Assessment of leg wound complications will be assessed at the time of discharge and at approximately six-week post-surgery during a clinic visit (this visit will take place between approximately 4 to 8 weeks post-surgery). Post-operative leg wound complication status (yes/no) will be determined based on these assessments.

For hypothesis 5: The Quality of Life (QoL) outcome measure will be the summary measures from the VR-12 instrument of health related quality of life as measured by the Physical Component Summary (PCS) and Mental Component Summary (MCS) and the Seattle Angina Questionnaire. QoL self-assessments will be completed at baseline, six weeks, and one year (by mail or telephone). Additionally, participants will be categorized as "improved", "no change", or "worsened" based on their baseline scores.

For hypothesis 6: Clinical measures include MACE.

2.3 Derived variables

2.3.1 Seattle Angina Questionnaire

The Seattle Angina Questionnaire (SAQ) is the leading health-related QoL measure for patients with coronary artery disease. The self-assessment questionnaire consists of a list of activities people often do during the week (e.g., dressing yourself, walking indoors on level ground, showering) and asks participants the amount of limitation (ranging from not at all limited to extremely limited) they have doing these activities due to chest pain, chest tightness, or angina over the previous 4 weeks. Additional questions ask about frequency and treatment of chest pain, chest tightness, or angina.

The answers provided on the SAQ are used to calculate scores in five scales: 1) Angina Stability, a measure of whether a patient's symptoms are changing over time; 2) Angina Frequency, a measure of how often a patient is having symptoms now; 3) Physical Limitation, a measure of how much a patient's condition is hampering his ability to do what he wants to do; 4) Treatment Satisfaction, a measure of well a patient understands her care and what she thinks of it; and 5) Quality of Life, a measure of the overall impact of a patient's condition on a patient's interpersonal relationships and state of mind. Participants will complete the SAQ at baseline, 6 weeks, and 1 year post-surgery. Higher scores are better. For follow-up assessments, participants will be categorized as "improved", "no change", or "worsened" based on their baseline scores.

2.3.2 VR-12

The Veterans RAND 12 Item Health Survey (VR-12) is a self-administered questionnaire with both physical and psychological domains using no more than 10 questions to create physical (PCS) and mental (MCS) component summary scores. The scoring of the PCS and MCS for the VR-12 is based on weights derived from the VR-36 instrument administered to 1.4 million Veteran enrollees with 877,775 respondents in the 1999 Large Health Survey of Veteran Enrollees (Veterans Health Study) (Iqbal et al. 2009). Higher PCS and MCS scores reflect greater quality of life. Imputation methods will be used to calculate scores for Veterans who do not complete all 12 questions included in this measure. Participants will complete the VR-12 at baseline, 6 weeks, and 1 year post-surgery. For follow-up assessments, change from baseline will be examined. Higher PCS and MCS scores reflect greater quality of life.

2.3.3 Syntax Score

The SYNTAX Score is a unique tool to score the complexity of coronary artery disease (available at www.syntaxscore.com). Higher scores are associated with greater risk.

2.3.4 VASQIP Score

The VA Surgical Quality Improvement Program (VASQIP) score will be used to assess 30-day surgical risk of mortality. Higher scores are associated with greater risk.

2.3.5 STS Score

The Society of Thoracic Surgeons (STS) score will be used to assess risk of operative mortality and morbidity of adult cardiac surgery on the basis of patient demographic and clinical characteristics. Higher scores are associated with greater risk.

2.3.6 Leg Incision Pain Impact Questionnaire

Severe leg pain, due to incisions made during vein grafting, data will be collected at discharge and at 4-6 weeks post-CABG. The Pain Impact Questionnaire (PIQ) is a 6-item measure of pain severity and its impact on health-related QoL (Becker et al. 2005). Impact scores range from 40 to 78 with higher scores reflecting greater pain impact. Scores can be groups into: 1) Little or No Impact (impact score $\leq$ 50); 2) Some Impact (50 < impact score $\leq$ 57); 3) Substantial Impact (57 < impact score $\leq$ 63); and 4) Severe Impact (impact score > 63). A pain severity rating is also calculated from the first PIQ item and ranges from 1 to 6, with severe pain defined as a score of 3 (mild) or above.

2.3.7 Leg Incision Assessment

The leg incision assessment calculates asepsis score based on information gathered at discharge and 4-6 weeks follow-up. At discharge ratings are given to the severity of serious exudates, erythema, purulent exudates, and separation of tissues. At follow-up, antibiotic use, drainage under local anesthetic, debridement under general anesthetic, bacterial isolation, hospital stay prolonged >14 days, development of pus as an outpatient, and visiting nurse visit to dress wound are assessed (Wilson et al. 1986). Then, responses are summed to create a total asepsis score.

2.3.8 Treatment Groups

Veteran patients will be randomized to receive one of two possible vein harvesting procedures:

- Open vein harvesting (OVH) – the traditional method of saphenectomy for CABG performed under direct vision using a single long incision or, more commonly, multiple smaller incisions (referred to as "bridging" technique) along the course of the vein. This approach minimizes manipulation and direct trauma to the conduit but is associated with potential for discomfort and leg wound healing complications.

- Endoscopic vein harvesting (EVH) – a minimally invasive procedure that was developed to eliminate the need for long incisions associated with OVH. EVH reduces the risk of wound infections and other leg wound complications but may be more traumatic to the conduit than OVH.

3 STUDY METHODS

3.1 General Study Design and Plan

This study is a randomized, intent-to-treat, two-arm, parallel design, multicenter study to compare clinical outcomes of major adverse cardiac events (MACE) of CABG patients treated with SVG harvested with EVH and OVH during the trial period. Cardiac Surgery Programs at Veterans Affairs Medical Centers (VAMCs) with expertise in performing both EVH and OVH are eligible to participate in the study (EVH Program established for more than two years and at least 100 successful EVH cases performed by each mid-level provider or other designated individual involved with the study) (Desai et al. 2011). Participants requiring elective or urgent CABG using cardiopulmonary bypass with use of at least one SVG will be screened using established inclusion/exclusion criteria. Participants will be randomized to one of the two arms (EVH or OVH) after an experienced vein harvester is identified and assigned to the case. Assessments will be collected at multiple time points including: baseline, intraoperatively, postoperatively, and at discharge or 30 days after surgery if still hospitalized. Assessment of leg wound complications will be completed at the time of discharge and at approximately six weeks post-surgery. Quality of life self-assessments will be completed at baseline, six weeks, and one year (by mail or telephone). Telephone follow-ups will occur at three-month intervals post-surgery until the participating centers are decommissioned at the end of the trial period (which would be approximately 4.5 years after the center initiations). For long-term MACE outcomes, passive follow-up for MACE using VA clinical and administrative databases (CPRS, VASQIP, etc.) will be performed centrally by the Study Chair's office for another 2 years. This study will enter approximately 1,150 participants in 16 participating VA medical centers.

3.2 Screening and Baseline Assessments

The research study coordinator will be primarily responsible for identifying each non-emergent patient scheduled for a CABG-only procedure with planned SVG harvesting. A diagnostic catheterization must be performed within six months prior to the scheduled operation to be used as part of the baseline assessments. The participating surgeon(s) must agree that the patient is eligible for either study arm before randomization based on the inclusion/exclusion criteria defined by the protocol. This includes a review of the medical history for any lower extremity issues that would prevent the harvest of an effective SVG such as varicose veins, etc. Following participant informed consent, the baseline risk assessment, clinical data and participant self-reported symptom status and health-related quality of life data will be obtained by the study team.

3.3 Inclusion-Exclusion Criteria

3.3.1 Participant Population

All participants who are candidates for CABG and who will undergo surgery at a VAMC with demonstrated expertise for both OVH and EVH and qualify to participate in CSP-sponsored research will be invited to participate in the REGROUP study.

3.3.2 Inclusion Criteria

1) Age 18 years or older

2) Elective or Urgent CABG-only
3) Median sternotomy approach
4) At least one coronary bypass planned using saphenous vein graft for conduit
5) Experienced EVH/OVH harvester and participating surgeon available for procedure

3.3.3 Exclusion Criteria

1) Combined valve procedure planned
2) Moderate or severe valve disease (see definition of moderate/severe valve)
3) Hemodynamically unstable or in cardiogenic shock
4) Enrolled in another therapeutic or interventional study
5) Off-pump CABG procedure planned
6) Limited life expectancy < 1 year
7) History of lower extremities venous stripping or ligation
8) Inability to provide informed consent

3.4 Randomization and Blinding

A block randomization scheme will be used to randomize participants in two treatment groups. The block randomization technique will ensure equal distribution of participants, within each harvester, within each medical center, in both arms of the trial. A random sequence of block sizes will be used to reduce the chances of guessing future allocations. The randomization schema will be generated using SAS (SAS, Cary, NC). All participating vein harvesters must meet the minimum EVH/OVH volume criteria [at least 100 EVH cases with low conversion rates (<5%) as part of an EVH program established for more than two years] to be eligible to enroll patients in this study. Unless an urgent medical condition exists, the participant's surgery will be scheduled to occur at the earliest possible date based on expert harvester availability and other center circumstances. The randomization procedure will occur after the participating expert harvester is assigned to the participant. Participants will be randomized within the assigned participating harvesters to one of the two study harvesting technique arms (EVH or OVH). Recognizing that the participant's assignment to a participating vein harvester will have already occurred, the study randomization to either EVH or OVH will be done by a telephone call to the Perry Point Cooperative Studies Program Coordinating Center (CSPCC).

3.5 Forms for Screening, Baseline, and Follow-up Visits

Baseline assessments will be collected prior to surgery and randomization. Intraoperative assessments will be collected during the CABG procedure, 24 and 48 hours postoperatively. Assessments will also be collected at the time of hospital discharge or 30 days post-surgery, whichever occurs first. Participants will return for a six-week clinic visit to assess the condition of their leg incision and healing status. Participants will receive a phone call every three months for follow-up for events until participant termination. Participants will complete QoL surveys again at one year either by telephone or mail. The following forms in Table 1 will be used during the screening, baseline, and follow-up visits of the study.

TABLE 1: Schedule of Assessments: Screening, Baseline, and Follow-up Data Forms

FORM	SCREEN	BASELINE (pre op) Visit 00	INTRA OP Visit 00	POST OP Visit 00	DC-30 DAY Visit 01	6 WK Visit 02	3 MO Visit 03	6 MO Visit 06	9 MO Visit 09	12 Mo Visit 12	… Every 3 Mo	45 MO Visit 45	49 MO Visit 49	AS NEEDED
00 – Screening Log	X													
01 – Screening and Randomization	X													
02 – Baseline Information		X												
03 – Seattle Angina Questionnaire		X				X				X	Mo 36 only Δ			
04 – VR-12		X				X				X	Mo 36 only Δ			
05 – Intraoperative Data Collection			X											
06 – Post Operative Assessments				X										
07 – Discharge Assessments					X									
08 –Leg Incision Pain Questionnaire					X									
09 – Leg Incision Pain 6 week						X								
10 – Leg Incision Assessment					X*	X*								
11 – Mace Event (6 week)						X								
12 – Phone Call Follow-up							X	X	X	X	X	X	X	
13 – MACE Event Form													X	
14 - Termination														X
15 - SAE														X
16 – SAE Follow-up														X
17 – Harvester Experience														X
18 – Protocol Noncompliance														X
19 – Confirmation of MI by Local														X
20 – Confirmation of MI by Clinical Events Committee														X
21 – Cause of Death by Clinical Events Committee														X
22 – Tobacco Use and CPB											Mo 36 only			
86 - Consent	X													

* Form 10 is collected at two time points (discharge & 6 weeks); do not fax form until the 6-week assessment has been completed.

Δ Per request from HERC, the VR-12 and SAQ at Month 36 have been added.

3.6 Sample Size

In the ROOBY study (CSP # 517) (Shroyer et al. 2009), 1-year MACE rates were 9.9% in the OVH group and 15.3% in the EVH group (p=0.0025). The executive committee for the REGROUP study assumed that during the REGROUP study, 15.5% of the participants in the EVH group will experience MACE in the first year post surgery. The committee also expects a 6 percentage point improvement in the 1-year MACE rate in the OVH group.

To detect the expected 6 percentage point difference in 1-year MACE rates between EVH (15.5%) and OVH (9.5%), a sample size of 545 in each group will be required at 85% power, 5% type-I error rate and with a two-sided test. Since, it would be possible to capture the majority of the MACE from the VA databases even if participants drop out before the one-year clinic visit, a relatively small inflation factor of 5% is used to inflate the sample size to account for the drop-outs. Thus, a total of 1,150 participants need to be randomized in the study to achieve the said power.

4 STUDY AND DATA MANAGEMENT

4.1 Study Management at the CSPCC

A Cooperative Studies Program Coordinating Center (CSPCC) study team has been assigned to this study for providing data management, statistical, and administrative supports to the study executive committee for a smooth conduct and timely completion of the study. The study team is comprised of:

Biostatistician and Team Lead	Eileen Stock, Ph.D.
Project Manager	Annette Wiseman
Statistical Programmer	Ellen DeMatt, M.A.
Database Programmers	Christine Dalzell
Computer Assistant	Daniel Briones
Computer Assistant	Mike Beam

Other core CSPCC staff, for example, Quality Assurance, Travel Clerk, Printer, Secretary, etc., will provide help based on the need of the study.

The Biostatistician is the study team leader and has the overall responsibility for the conduct of the study at the CSPCC. S/he is the CSPCC's spokesperson to the Study Group; s/he represents the CSPCC on the study's Executive Committee and along with the Study Chairpersons, she is responsible for representing the study at the Data Monitoring Committee meetings. The Biostatistician is also responsible for providing the Study Group with statistical and clinical trial advice, for working with other CSPCC team members in the preparation of routine interim reports, and for conducting the final analyses at the end of the study.

The Project Manager is responsible for the administrative coordination of the study by the CSPCC. S/he serves as the Biostatistician's Administrative Assistant and works with the CSPCC study team to ensure that all reports, study materials, and meeting arrangement notices are sent to the proper individuals in a timely fashion. S/he will work closely with the National Study Coordinator in the Chairman's office to ensure that the study runs smoothly and will be in contact with both the National Study Coordinator and the Local Research Coordinators at the participating centers at least monthly to discuss any problems that they may be having, including those with the CSPCC. S/he will also work with the local VA R&D Offices at the participating centers to obtain R&D and IRB approvals at the beginning of the study and annually as well as the preparation of study budgets yearly during the ongoing phases of the study.

The Statistical Programmer is responsible for the preparation of the tables and analyses for all of the routine study reports. These include Study Group, Executive Committee, Data Monitoring Committee, and the mid-study report to CSSEC. S/he also prepares the tables and reports for the final analyses. S/he works closely with the Biostatistician on these analyses.

The Database Management System (DBMS) Programmer is the lead of the data management support group and works closely with the assigned computer assistant(s) to address the data management need for the assigned study. S/he is responsible for establishing, updating and maintaining the study's database. In addition, s/he will write edit program based on an agreed upon edit plan that will thoroughly check the data for errors and missing information. S/he is also responsible for programming and maintaining the randomization system for the study.

The Computer Assistant(s) are responsible for setting up the data definition table for the study, for building the Study Definition Editor and also for laying out the electronic case report forms in the form design software. They are also responsible for training the study staff at each site on how to properly manage the data collection process and how to appropriately respond to data edits. The computer assistant(s) are also responsible for working with the sites to resolve the data queries generated based on the incomplete and/or inaccurate data submitted to the study database.

4.2 Randomization and Data Management

Randomization and data management will be performed by the Perry Point CSPCC. An Interactive Touchtone Telephone Randomization System (ITTRS) will be used to set up the randomization system. Clinical DataFax System, a data management software will be used for data management. The CSPCC will have overall responsibility for the data at the end of the study.

After a patient at any of the participating centers is consented, successfully screened and has provided baseline information, s/he will be assigned to a harvester. Once a harvester is assigned and available for the harvesting of the required vein, the patient will be randomized. The research coordinator will place a

call to the ITTRS (a dedicated 1-800 phone number will be provided) to randomize the patient in one of the two harvesting techniques – endoscopic and open vein harvesting techniques. Once the required information is entered in the system, the system will return the assignment for the patient. This study will use a "permuted block" randomization scheme where random block sizes of two and four will be used. The research coordinator will need the following information in order to complete a successful randomization call:

a. Study number and study password (will be provided by CSPCC)
b. 3-digit site number and password (will be provided by CSPCC)
c. The participant's ID Number & ALPHA Code
d. The participant's signed Informed Consent Form
e. Form 01, Screening and Randomization
f. Laminated Randomization Cheat Sheet

The system for data capturing will be designed by visits where a group of required case report forms (CRFs) will be assigned to each "visit" according to the "Schedule of Assessments" that was provided in Table 1.

When a participating site has a potential study participant that meets all of the eligibility requirements, the site investigator (SI) or site coordinator (SC) (or other local study team member designee) will assign a unique participant ID and Alpha code to the participant. This unique Participant ID number and alpha code will be entered on all study related-forms for the duration of the study.

Paper CRFs will be mailed to the sites. The research personnel will be completing the CRFs during CABG, the 6-week clinic visit, and the 3-month phone calls. The completed CRFs will then be scanned in pdf and sent to Perry Point CSPCC via secure electronic server or posted on an ftp server. The DataFax system will have built-in edit checks on data fields to minimize data errors, such as missing, inconsistent, or extremely unusual data. At CSPCC, the data management section staff will validate the CRFs once received by the DataFax system and will generate QC reports listing data discrepancies and other irregularities at regular intervals. These QC reports will be sent to the respective sites for clarifications and the site personnel will then submit "Refaxes" with clarification which will be validated and committed to the study master database (A "Refax" is a page of a CRF with corrections which is sent back to the CSPCC by agreed upon mode of CRF transmission). The final responsibility for the completeness and accuracy of all study data collected at a participating site resides with the SI who will review all data before submission. The study database will be continuously updated with new data and changes to previously submitted data. To notify the participating sites about missing or late forms, reports with pertinent information will be generated at a regular interval and will be posted on a site-accessible sub-SharePoint site.

In addition, a summary report of all data submitted and problems identified will be generated for each participating site. This report will provide each site with a summary of their progress. The National Study Coordinator in the Chairman's Office will also be reviewing each site's progress to ensure that there are no unforeseen problems with the forms or with a particular participant.

Another mechanism used to monitor the data and the progress of the study will be the preparation of periodic reports for various groups who are responsible for overseeing the conduct of the study. These groups include the Study Group, the Executive Committee, the Data Monitoring Committee, and the CSPCC Human Rights Committee, if applicable.

5 GENERAL CONSIDERATIONS

5.1 Timing of Analyses

The Study Group, which consists of all site investigators, participating harvesters, and research coordinators, will meet annually to discuss the progress of the study and any problems encountered during the conduct of the trial. These reports will contain information on:

- Screening, Enrollment, and Retention
- Participant background characteristics at entry
- Data quality and protocol adherence

The groups charged with monitoring the various aspects of the study will be the Executive Committee, the Data Monitoring Committee (DMC), and the local site IRBs. These committees will meet at regular intervals according to the current Cooperative Studies Program guidelines: prior to the beginning of patient enrollment and at least every twelve months thereafter.

The final analysis will be performed on data which will have been documented as meeting the cleaning and approval requirements of CSP SOPs and after the finalization and approval of this SAP document.

5.2 Analysis Populations

Any participant requiring a non-emergent CABG will be considered for entry into the study. Participants who are hemodynamically unstable, have moderate to severe valvular disease or are unwilling or unable to provide informed consent will be excluded. The exact process for assigning the statuses will be defined and documented prior to final analyses along with any predefined reasons for eliminating a participant from a particular population.

<u>Intent-to-Treat (ITT)</u>

This population includes all participants who are randomized to the study. Participants will be assigned for analysis according to the group to which they were randomized, OVH or EVH. Participants will be categorized (in terms of their harvesting technique group assignment) based on their initial randomized group irrespective of conversion before surgery and will be included in the analyses irrespective of their status – completer or drop out of the study before completion. Analysis of all outcome measures – primary, secondary, and tertiary – will use the ITT population.

Safety

This population includes all participants who have signed informed consent. Adverse events are recorded for the duration of the participant's study participation and may include serious adverse events for up to one month after participation ends.

5.3 Missing Data and Imputations

Every effort will be made to minimize the occurrence of missing data, particularly for the primary and main secondary outcome measures. For the primary outcome (MACE), every effort will be made to contact the participants over the phone every three months until participant termination. In the event of a potential drop out, every effort will be made to capture the MACE data from the VA databases. The primary analyses will analyze the data as observed. When missing data are encountered in the analyses, a detailed sensitivity analysis may be conducted of the effects of various assumptions about the missing data and imputation methods utilized.

5.4 General Considerations

This section details general policies to be used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

- All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any p-value $\leq \alpha$ will be considered statistically significant and will be marked with one asterisk (e.g., 0.026*).
- Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, and maximum for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value.

- All percentages will be rounded to one decimal place. The number and percentage of responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The decimal of the percentage may be dropped due to space constraints when creating a table.
- All listings will be sorted for presentation in order of treatment group, site number, participant number, and date of procedure or event.
- When necessary for analysis purposes, partial dates will be completed (i.e., turned into complete dates) using the most conservative approach.
- All analysis and summary tables will have the population sample size for each group or treatment group in the column heading.
- Version 9.3 of SAS® or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.
- Updated version of MedDRA will be used for adverse event and pre-treatment coding.
- The current version of the World Health Organization (WHO) drug dictionary will be used for the coding of medications.

5.5 Interim Monitoring

An independent oversight committee, a Data Monitoring Committee (DMC), will be monitoring study progress at predetermined time points over the entire duration of the study. The committee will receive analyses of the primary outcome measures and the important secondary outcome measures on a routine basis. In general, this committee meets at six to nine months after the start of subject recruitment and yearly thereafter. So, in total, this committee will meet maximum four times during the four years of the study duration. The committee will receive reports about three weeks prior to their annual meetings and at six monthly intervals in between the annual meetings. Since the primary outcome measure (MACE) is time-to-MACE event, sufficient data for DMC's first review will not be available until the study has been ongoing for at least 2 years. So there will be approximately 8 interim analyses of the primary outcome measure based on which the DMC will decide on study's continuation.

5.5.1 Data Monitoring Committee

An independent oversight committee called the Data Monitoring Committee (DMC) will monitor study progress. This committee meets on the same basic schedule as the Study Group and Executive Committee, i.e., at 6 to 9 months after the start of participant recruitment and yearly thereafter. Initially, the DMC will meet to become acquainted with the study and to establish monitoring guidelines.

The main responsibility of the DMC members is to make a recommendation to the Director of the Cooperative Studies Program on whether the study should continue or not based on the reviews of the progress reports submitted to them. The study could be recommended for termination due to poor recruitment, treatment differences so large that it would be possible to reach a final decision about the main question of the study, treatment differences so small that continuation would be irresponsible, or

due to safety concerns. The DMC also reviews the participating sites' performance in terms of recruitment, adherence to the protocol etc., and makes recommendations on them. Their final responsibility is to review all proposed protocol changes and suggested sub-protocols and to make recommendations in regards to their acceptability.

In order for the DMC to carry out its responsibilities, the CSPCC Study Team will provide the committee with a report approximately three weeks prior to their meetings. The report will consist of the tables describing number of participants enrolled, study progress, baseline demographics, as well as tables presenting outcome analyses. It is the responsibility of the CSPCC Study Team to provide the DMC with whatever information the committee feels that it needs to successfully monitor the study. Thus, additional tables will be added as required by the DMC. In addition to the reports for the yearly meetings, the DMC will also be provided with reports between meetings at 6-month intervals.

The patient characteristics would be presented by medical center and by harvesting technique group for the DMC. Significant imbalances of these patient characteristics between the harvesting technique groups may indicate a need to use these characteristics as covariates during the analysis of the outcome measures. Formal testing of the differences between groups will be done at the study's conclusion using appropriate statistical tests - analysis of variance technique will be used to test characteristics that are continuous in nature, while chi-square technique will be used for the test characteristics that are discrete in nature.

As with any clinical trial, the safety of the patient will be of utmost concern. Safety will be monitored closely during the course of the study. The DMC Report will include data on incidence of adverse events by treatment group. It will also include data on early terminations and treatment dropouts. The adverse event data will also be reported in the primary study manuscript. Data will be collected on adverse events throughout the study starting immediately after the patient signs the informed consent form.

5.5.1.1 Stopping Rules

In order for the DMC to make its recommendation for continuation of the study, it will be necessary for them to see the analyses for the primary outcome measure every time that the report is run and it is possible to calculate the primary outcome measure. Periodic monitoring of interim results can significantly affect the probability of making an incorrect decision. A number of formal techniques have been developed for interpreting interim results. At the organizational meeting, the DMC will select the technique that it wants to use to monitor the study. Suggested techniques are the Haybittle-Peto and Lan-DeMets group sequential boundaries. For the Haybittle-Peto method, a constant z-statistic is used as the monitoring boundary. The Lan-DeMets procedure produces decision boundaries that are quite conservative over the first several looks and then gradually converges to the nominal alpha levels as the final look is approached. The DMC will also analyze the safety data from the study to determine if the study should terminate. This will continue throughout the study.

5.5.2 Executive Committee

The Executive Committee is the management and decision-making body for the operational aspects of the study and will monitor the performance of participating medical centers and the quality of data collected. The Executive Committee will formulate publication plans and will oversee the publication and presentation of all data from the study. The Committee must grant permission before any study data may be used for presentation or publication. The Executive Committee is comprised of the Chairmen, PPCSP Biostatistician and Project Manager, LSIs and Subject Matter Experts.

6 SUMMARY OF STUDY DATA

All continuous variables will be summarised using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum and minimum. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, data listed will be sorted by medical center, treatment, and participant or by medical center and participant. Summary tables including treatment will be structured with either a column for each treatment in the order (OVH, EVH) or as rows for each treatment in the same order. Each table will be annotated with the total population size relevant to that table/treatment, including any missing observations.

6.1 Subject Disposition

Participant disposition will be summarized for all participants that signed the consent form and for the randomized population. The following data will be presented:

- The number of participants screened, eligible, consented, randomized, and expected to be randomized by medical center (TABLE 2). This table also provides the number of participants randomized to each group by center.
- The number of participants screened and randomized by month for each medical center (TABLE 3).
- A figure of participants randomized and expected by month (FIGURE 1).
- A listing that will include the reasons for exclusion of participants who discontinued from the study. These will include reasons for ineligibility (TABLE 4), non-enrollment (TABLE 5), and non-randomization (TABLE 6).
- Participant disposition by medical center for all participants (TABLE 7).

6.2 Demographics

Demographic characteristics at baseline will be summarized for all study participants. Demographic characteristics of all study participants will include age, gender, race/ethnicity, marital status, and education. The summary will include:

- The number and percentage of participants with each category of gender, race/ethnicity, marital status, and education (TABLE 8).
- The sample size, mean, median, SD, minimum and Maximum values for the following:
    - Age – calculated using the participant's birth date (birth date on Form 01).

Estimates of the baseline demographic characteristics will be presented for all study participants. Tables summarizing the important background characteristics by medical center and treatment will be prepared and submitted to the Study Group to provide an idea of the population being studied, and based on this information, comparisons of the participant characteristics among the centers will be possible.

6.3 Baseline Variables

6.3.1 Seattle Angina Questionnaire

The sample size, mean, median, SD and minimum and maximum values for the 5 component scores including angina stability, angina frequency, physical limitation, treatment satisfaction, and quality of life will reported for the baseline visit, overall by medical center and treatment (TABLE 9).

6.3.2 VR-12

The sample size, mean, median, SD, minimum, and maximum values for the PCS and MCS scores from the VR-12 will be presented for the baseline visit, overall by medical center and treatment (TABLE 10).

6.3.3 Conversion to Open Harvest Procedure

The conversion rate from EVH to OVH among randomized participants will be presented, overall and by medical center and harvester (TABLE 11), along with a list of reasons by center for the conversion (TABLE 12). The conversion rate, excluding conversions completed because the unanticipated graft required an additional vein will also be reported (TABLE 13).

6.3.4 Complexity of Coronary Artery Disease and Mortality and Morbidity Risks

The sample size, mean, median, SD, minimum, and maximum values for Syntax scores, indicating the complexity of coronary artery disease (CAD), will be presented, overall and by medical center, by MACE type, by age group, and by diabetes status as well as by treatment group (TABLES 14-17). Similar tables will be produced for the mortality and morbidity risk measures, VA Surgical Quality Improvement Program (VASQIP) and STS risk of mortality.

6.3.5 Bilateral Mammary Artery Grafting

The rate of bilateral mammary artery grafting among randomized participants will be presented, overall and by medical center (TABLE 18).

6.3.6 Leg Incision Healing and Severity of Incisional Leg Pain

The rate of leg incision infection and disturbance, along with severity of incisional leg pain (little or no impact, some impact, substantial impact, or severe impact) at discharge and 6-weeks will be assessed, overall and by medical center (TABLES 19-20).

6.4 Treatment Exposure

Treatment exposure is the vein harvesting technique to which study participants are randomized to, OVH vs. EVH. The number and percentages of participants randomized to either OVH or EVH will be reported.

- OVH – the traditional method of saphenectomy for CABG. It is performed under direct vision using a single long incision or, more commonly, multiple smaller incisions (referred to as "bridging" technique) along the course of the vein. This approach minimizes manipulation and direct trauma to the conduit but is associated with potential for discomfort and leg wound healing complications.
- EVH – is a minimally invasive procedure that was developed to eliminate the need for long incisions associated with OVH. EVH reduces the risk of wound infections and other leg wound complications but may be more traumatic to the conduit than OVH.

6.5 Study Endpoint

The rate of MACE and its components (all-cause mortality, nonfatal myocardial infarction, & repeat revascularization) will be reported, overall and by treatment (TABLE 21). Mean length of follow-up (in days) will also be reported by medical center and treatment (TABLE 22).

6.6 MACE by Harvester Experience

6.6.1 MACE by General Experience

The rate of MACE and its components (all-cause mortality, nonfatal myocardial infarction, & repeat revascularization) will be reported by harvesters' general experience: < 5 years, > 5 but < 10 years, and > 10 years. A separate table (similar to TABLE 21) will be provided for each level of experience.

6.6.2 MACE by EVH Experience

The rate of MACE and its components (all-cause mortality, nonfatal myocardial infarction, & repeat revascularization) will be reported by harvesters' EVH Experience: > 100 but < 500, > 500 but $< 1{,}000$, $> 1{,}000$ but $< 2{,}000$, and $>2{,}000$ endoscopic vein harvests completed. A separate table (similar to TABLE 21) will be provided for each level of experience.

6.6.3 MACE by OVH Experience

The rate of MACE and its components (all-cause mortality, nonfatal myocardial infarction, & repeat revascularization) will be reported by harvesters' OVH Experience: < 50, > 50 but < 100, > 100 but < 500, > 500 but < 1,000, >1,000 but < 2,000, and >2,000 endoscopic vein harvests completed. A separate table (similar to TABLE 21) will be provided for each level of experience.

6.7 Serious Adverse Events

Serious adverse event (SAE) incidence using MedDRA coding after randomization will be reported by body system and preferred term, overall and by treatment (TABLE 23).

6.8 Protocol Non-compliance

A listing of protocol non-compliance by medical center will be provided (TABLE 24).

7 STATISTICAL ANALYSES

7.1 Primary Outcome

The primary objective of this study is to investigate the impact of SVG harvesting techniques – OVH vs. EVH on MACE, a composite end point of all-cause mortality, nonfatal myocardial infarction and repeat revascularization, over the active follow-up period of the study postoperatively. The active follow-up time would begin with the first randomized patient and end after the last participant randomized has reached at least one-year of follow-up. Assuming the enrollment period is approximately three years, this would equate to approximately 4 to 4.5 years of active follow-up (in-clinic visit or contact by telephone carried out by site personnel), which will also be followed by two years of passive follow-up (carried out centrally by the chair's office staff using VA administrative databases). Thus, total follow-up time (active and passive) would be approximately 6.5 years. The primary outcome in the study is time (from index CABG surgery date) until the event of interest, MACE, or time-to-MACE during active follow-up (~4.5 years). Only the first event among participants will be considered as the MACE event.

To begin the analyses, the rate of MACE and its components (all-cause mortality, nonfatal myocardial infarction, & repeat revascularization) during active follow-up will be reported, both collectively and by SVG harvesting technique, OVH vs. EVH, considering only the first event so that components sum to total MACE (similar to TABLE 21). Survival analysis techniques will be employed to analyze the time-to-MACE data. Participants who are either lost-to-follow-up or did not experience a MACE event during the active follow-up period will be considered right-censored. Kaplan-Meier nonparametric survival estimates for risk of MACE will depict the unadjusted impact of SVG harvesting technique on MACE (FIGURE 2). Survival time represents time not experiencing a MACE. Tests of

equality (null hypothesis) of the survival function estimates across strata (OVH and EVH) will employ either the log-rank or Wilcoxon test. Multivariable survival analyses applying a Cox proportional hazards regression model will be performed to investigate the effect of SVG harvesting technique on time-to-MACE, adjusting for other potentially influential baseline characteristics, such as age, gender, harvester's experience, etc. (TABLE 25). Assumptions of the model (i.e., non-informative censoring, proportional hazards) will be checked. If assumptions appear to be violated, alternative methods will be explored (e.g., piecewise, time-varying covariates). A type I error rate of $\alpha = 0.05$ will be used throughout. Confidence intervals will be two-sided with a 95% confidence level.

The hypothesis for the primary aim of this study is:

> *H1: A significantly smaller proportion of CABG subjects with SVGs harvested by open technique will experience MACE post-surgery compared to CABG subjects with SVGs harvested by endoscopic technique during the active follow-up period.*

The hypothesis for the primary aim of this study will be supported when an increased risk of MACE is observed among participants randomized to EVH, confirmed with a hazards ratio (HR) > 1.00 for EVH vs. OVH and a significant corresponding *p-value* < α.

7.2 Secondary Outcomes

Secondary objectives of this study include investigating the impact of SVG harvesting techniques – OVH vs. EVH on MACE at one and three-years postoperatively and over the entire follow-up period (active and passive, ~6.5 years) of the study postoperatively. The proportion of participants experiencing a MACE (yes/no) in the first year of follow-up after index CABG surgery date will be calculated, both collectively and by SVG harvesting technique, OVH vs. EVH. These two proportions will be compared using Pearson's chi-square test. The proportion of participants experiencing a MACE (yes-1/no-0) in the three years of follow-up after index CABG surgery date will be similarly analyzed (TABLE 26).

Assessing MACE over the entire follow-up period (active and passive) of the study postoperatively will be analyzed similarly (TABLE 21, FIGURE 2, TABLE 25) to the primary outcome with now the outcome being time (from index CABG surgery date) until the event of interest, MACE, or time-to-MACE during the entire follow-up (~6.5 years). Events from both the active and passive follow-up periods will be considered, whereas the primary analysis only included events from the active follow-up period. Only the first event among participants will be considered as the MACE event.

The hypotheses for the secondary aims of this study are:

> *H2: One-year composite MACE rate will be 6 percentage points lower in the open harvesting group and three-year composite MACE rates will be at least 8-10 percentage points lower in the open vein harvesting group compared to the endoscopic vein harvesting group.*

H3: A significant smaller proportion of CABG subjects with SVGs harvested by open technique will experience MACE post-surgery compared to CABG subjects with SVGs harvested by endoscopic technique during the entire follow-up period.

The hypothesis H2 will be supported when the percent of participants experiencing MACE at one-year is 6% and at least 8% greater at three-years among those randomized to EVH vs. OVH, with a significant corresponding *p-value* < α observed for each test. The hypothesis H3 will be supported when an increased risk of MACE is observed among participants randomized to EVH, confirmed with a hazards ratio (HR) > 1.00 for EVH vs. OVH and a significant corresponding *p-value*. A total (recurrent) event analysis at various time points will also be explored comparing EVH and OVH.

7.3 Tertiary Outcomes

Tertiary objectives of this study include investigating the impact of SVG harvesting techniques – OVH vs. EVH on leg wound complication, patient satisfaction, and quality of life in addition to determining the role of vein harvester's experience on clinical outcomes.

All participants will be examined for post-operative complications of the leg wound from harvesting at discharge and at six weeks post-surgery. Post-operative leg wound complication status (yes-1/no-0) will be determined. The proportion of participants with leg wound complications will be computed for each treatment group and these proportions will be compared using Pearson's chi-square test (TABLE 27). The impact of confounding variables, such as BMI, diabetes status, and smoking status, on post-operative leg wound infection will be analyzed using multivariable logistic regression (TABLE 28). Surgical site infections at the vein harvest site according to the Center for Disease Control criteria will be explored.

Patient satisfaction will be assessed using the "Treatment Satisfaction" scale of the Seattle Angina Questionnaire. Participants will be categorized as "improved", "no change" and "worsened" at 6 weeks and 12 months compared to their baseline scores (TABLE 29). The proportion of participants in these three categories will be compared between the two groups using Pearson's chi-square test. The actual scores from these measures will also be used to compare harvesting techniques using analysis of covariance (ANCOVA) techniques, where the baseline (pre-surgery) scores will be used as a covariate (TABLE 30).

The occurrence of severe leg pain, due to incisions made during vein grafting, will be collected at discharge and 4-6 weeks post-CABG. The proportion of participants with severe pain (yes = pain severity rating score ≥ 3) at each time point will be compared across groups using Pearson's chi-square test (TABLE 31).

Quality of life scores using the PCS and MCS of the VR-12 and the "Quality of Life" scale of the Seattle Angina Questionnaire will be computed at baseline, six weeks, and 12 months post-surgery for participants in each SVG harvesting group. For each component of the VR-12 (PCS and MCS), mean changes from baseline at six weeks and 12 months will be computed and compared using ANCOVA (TABLE 32).

For each scale of the SAQ (angina stability, angina frequency, physical limitation, treatment satisfaction, & quality of life), participants will be categorized as "improved", "no change" and "worsened" at 6-weeks and 12 months compared to their baseline scores (TABLE 29). The proportion of participants in these three categories at each time point will be compared between the two groups using Pearson's chi-square test. The actual scores from these measures and that of the VR-12 MCS and PCS will be used to compare harvesting techniques using ANCOVA techniques, where the baseline (pre-surgery) scores will be used as a covariate (TABLE 30).

The hypotheses for the tertiary aims of this study are:

H4: Leg wound complications will be lower and satisfaction will be higher in the EVH group compared to OVH group.

H5: Subjects' quality of life scores will be higher in the EVH group compared to the OVH group.

H6: Exploratory Aim with no hypothesis specified.

The leg wound complication component of hypothesis H4 will be supported when the percent of participants experiencing leg wound complications randomized to EVH is lower than that of participants randomized to OVH with a significant *p-value* observed. Higher patient satisfaction in the EVH group vs. OVH group will be supported by a significant effect for treatment when entered into the ANCOVA model and a positive coefficient for EVH vs. OVH. The hypothesis H5 will be supported by a significant effect for treatment when entered into the ANCOVA model and a positive coefficient for EVH vs. OVH for the outcomes of SAQ quality of life scale, VR-12 PCS, and VR-12 MCS.

8 SERIOUS ADVERSE EVENTS

In this study, information on all serious adverse events (SAEs) will be collected and recorded. Incidence of SAEs will be summarized for each treatment group by body system and MedDRA term. The number and percentage of participants with each body system and MedDRA term will be presented for each treatment group.

9 STATISTICAL PROGRAM VALIDATION PLAN

Perry Point Work Instruction (WI) 202 – Validation Plan for SAS Statistical Programs will serve as the validation plan for validation of the statistical programs created for the analyses of data collected during this study.

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APPENDIX 1: TABLES AND FIGURES

TABLE 2: Number of Participants Screened, Eligible, Consented, Randomized and Expected Randomized, Total and by Medical Center

	Alb. (501)	Boston (523)	Cle. (541)	Miami (546)	Durham (558)	Gaines. (573)	Houston (580)	Minn. (618)	New York (630)	Asheville (637)	Pitts. (646)	Portland (648)	San Fran. (662)	Tampa (673)	Tucson (678)	Milw. (695)	Total
Number Screened																	
Ineligible																	
Percent Ineligible (of Screened)																	
Number Eligible																	
Not Consented																	
Percent Not Consented (of Eligible)																	
Number Consented																	
Not Randomized																	
Percent Not Randomized (of Consented)																	
Number Randomized																	
Expected																	
Percent of Expected																	
Randomized to OVH																	
Randomized to EVH																	

TABLE 3: Participants Screened and Randomized by Month, Total and by Medical Center

Month	Albuquerque (501)		Boston (523)		Cleveland (541)		Miami (546)		Durham (558)		Gainesville (573)	
	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized
Month 1												
Month 2												
Month 3												
Month 4												
Month 5												
Month 6												
Month 7												
Month 8												
Month 9												
Month 10												
Month 11												
Month 12												
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Month 28												
Month 29												
Month 30												
Month 31												
Month 32												
Month 33												
Month 34												
Month 35												
Month 36												
Month 37												
Month 38												

Month	Houston (580)		Minneapolis (618)		New York (630)		Asheville (637)		Pittsburgh (646)		Portland (648)	
	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized
Month 1												
Month 2												
Month 3												
Month 4												
Month 5												
Month 6												
Month 7												
Month 8												
Month 9												
Month 10												
Month 11												
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Month 32												
Month 33												
Month 34												
Month 35												
Month 36												
Month 37												
Month 38												

Month	San Francisco (662)		Tampa (673)		Tucson (678)		Milwaukee (695)		Total	
	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized	Screened	Randomized
Month 1										
Month 2										
Month 3										
Month 4										
Month 5										
Month 6										
Month 7										
Month 8										
Month 9										
Month 10										
Month 11										
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Month 36										
Month 37										
Month 38										

FIGURE 1: Randomization Activities Based on Number of Active Centers per Month

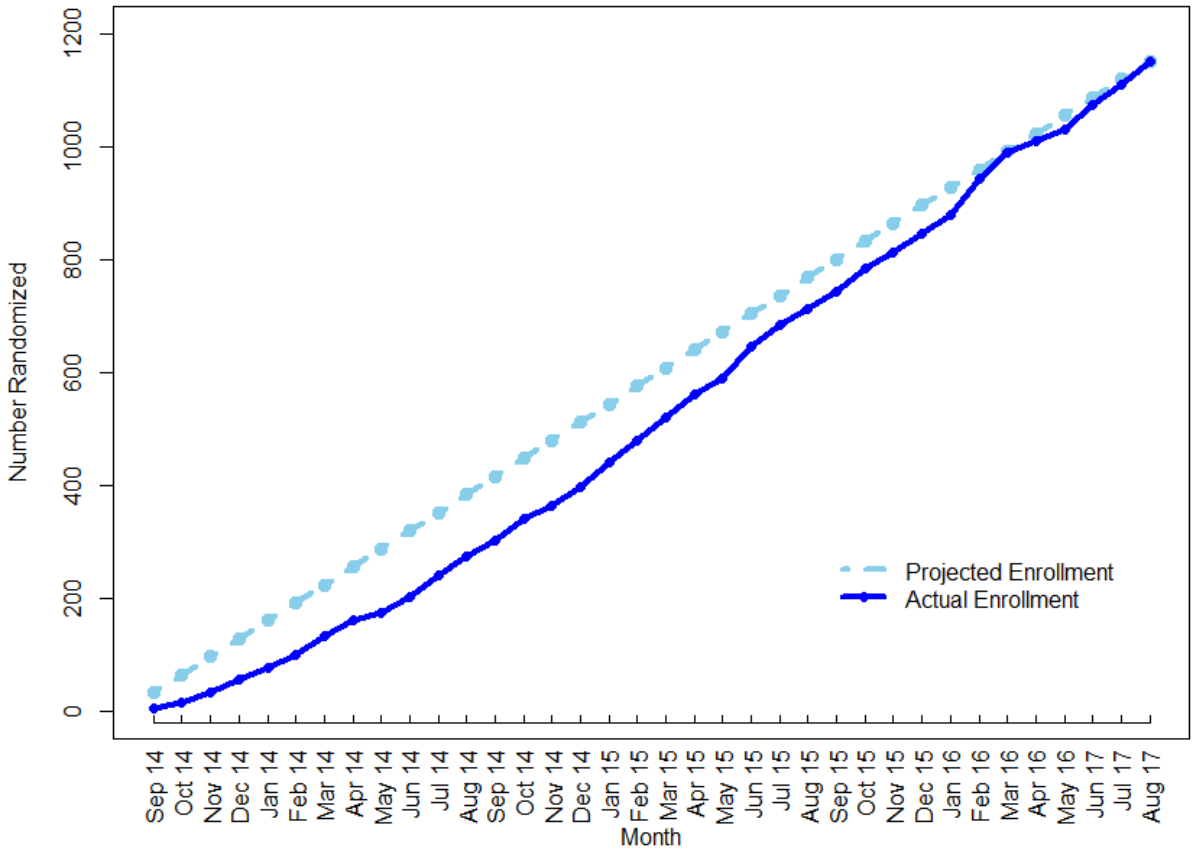

TABLE 4: Reasons for Ineligibility, Total and by Medical Center

	Alb. (501)	Boston (523)	Cle. (541)	Miami (546)	Durham (558)	Gaines. (573)	Houston (580)	Minn. (618)	New York (630)	Asheville (637)	Pitts. (646)	Portland (648)	San Fran. (662)	Tampa (673)	Tucson (678)	Milw. (695)	Total
Not elective or urgent CABG																	
Not median sternotomy approach																	
No coronary bypass planned using saphenous vein graft for conduit																	
No experienced EVH/OVH harvester and/or participating surgeon available for procedure																	
Combined valve procedure planned																	
Moderate or severe valve disease																	
Hemodynamically unstable or in cardiogenic shock																	
Enrolled in another therapeutic or interventional study																	
Off-pump CABG procedure planned																	
Limited life expectancy less than 1 year																	
History of lower extremities venous stripping or ligation																	
Inability to provide informed consent																	
Total																	

TABLE 5: Reasons for Non-Enrollment, Total and by Medical Center

	Alb. (501)	Boston (523)	Cle. (541)	Miami (546)	Durham (558)	Gaines. (573)	Houston (580)	Minn. (618)	New York (630)	Asheville (637)	Pitts. (646)	Portland (648)	San Fran. (662)	Tampa (673)	Tucson (678)	Milw. (695)	Total
Subject refused to sign Informed Consent																	
Eligibility status changed																	
Site surgeon concerned about resources needed for on-site follow-up																	
No reliable method of follow-up contact with the subject																	
Subject prefers open vein harvest																	
Subject prefers endoscopic vein harvest																	
Subject preferred non-enrollment for reasons other than vein harvest preference																	
Surgeon prefers open vein harvest for subject																	
Surgeon prefers endoscopic vein harvest for subject																	
Surgeon preferred non-enrollment for reasons other than vein harvest preference																	
Total																	

TABLE 6: Reasons for Non-Randomization, Total and by Medical Center

	Alb. (501)	Boston (523)	Cle. (541)	Miami (546)	Durham (558)	Gaines. (573)	Houston (580)	Minn. (618)	New York (630)	Asheville (637)	Pitts. (646)	Portland (648)	San Fran. (662)	Tampa (673)	Tucson (678)	Milw. (695)	Total
Eligibility status changed																	
Subject changed mind																	
Surgeon changed mind																	
Other reason																	
Total																	

TABLE 7: Status of Randomized Participants, Total and by Medical Center

Center	Randomized	Completed Week 6	In Active Follow-up	Early Termination*	Completers
Albuquerque (501)					
Boston (523)					
Cleveland (541)					
Miami (546)					
Durham (558)					
Gainesville (573)					
Houston (580)					
Minneapolis (618)					
New York (630)					
Asheville (637)					
Pittsburgh (646)					
Portland (648)					
San Francisco (662)					
Tampa (673)					
Tucson (678)					
Milwaukee (695)					
Total					

*****Reasons for early termination include: n (%) voluntarily withdrew, n (%) lost to follow-up, n (%) Other, and n (%) died.*

TABLE 8: Summary of Demographics, Total and by Medical Center

		Albuquerque (501)	Boston (523)	Cleveland (541)	Miami (546)	Durham (558)	Gainesville (573)
Age	n						
	Mean (SD)						
	Median						
	Min, Max						
Gender	n						
Male	n (%)						
Female	n (%)						
Race	n						
American Indian or Alaskan Native	n (%)						
Asian or Pacific Islander	n (%)						
Black, not of Hispanic origin	n (%)						
Hispanic	n (%)						
White, not of Hispanic origin	n (%)						
Other	n (%)						
Marital Status	n						
Married/remarried	n (%)						
Divorced	n (%)						
Separated	n (%)						
Widowed	n (%)						
Never married	n (%)						
Education	n						
Completed graduate/professional training	n (%)						
Standard college/university graduate	n (%)						
Partial college training	n (%)						
High school graduate/GED	n (%)						
< High school	n (%)						

		Houston (580)	Minn. (618)	New York (630)	Asheville (637)	Pitts. (646)	Portland (648)
Age	n						
	Mean (SD)						
	Median						
	Min, Max						
Gender	n						
Male	n (%)						
Female	n (%)						
Race	n						
American Indian or Alaskan Native	n (%)						
Asian or Pacific Islander	n (%)						
Black, not of Hispanic origin	n (%)						
Hispanic	n (%)						
White, not of Hispanic origin	n (%)						
Other	n (%)						
Marital Status	n						
Married/remarried	n (%)						
Divorced	n (%)						
Separated	n (%)						
Widowed	n (%)						
Never married	n (%)						
Education	n						
Completed graduate/professional training	n (%)						
Standard college/university graduate	n (%)						
Partial college training	n (%)						
High school graduate/GED	n (%)						
< High school	n (%)						

		San Fran. (662)	Tampa (673)	Tucson (678)	Milw. (695)	Total	OVH	EVH
Age	n							
	Mean (SD)							
	Median							
	Min, Max							
Gender	n							
Male	n (%)							
Female	n (%)							
Race	n							
American Indian or Alaskan Native	n (%)							
Asian or Pacific Islander	n (%)							
Black, not of Hispanic origin	n (%)							
Hispanic	n (%)							
White, not of Hispanic origin	n (%)							
Other	n (%)							
Marital Status	n							
Married/remarried	n (%)							
Divorced	n (%)							
Separated	n (%)							
Widowed	n (%)							
Never married	n (%)							
Education	n							
Completed graduate/professional training	n (%)							
Standard college/university graduate	n (%)							
Partial college training	n (%)							
High school graduate/GED	n (%)							
< High school	n (%)							

TABLE 9: Seattle Angina Questionnaire: [*Component scale here*] at Baseline, by Medical Center and Treatment

Center	OVH						EVH						Total					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Albuquerque (501)																		
Boston (523)																		
Cleveland (541)																		
Miami (546)																		
Durham (558)																		
Gainesville (573)																		
Houston (580)																		
Minneapolis (618)																		
New York (630)																		
Asheville (637)																		
Pittsburgh (646)																		
Portland (648)																		
San Francisco (662)																		
Tampa (673)																		
Tucson (678)																		
Milwaukee (695)																		
Total																		

TABLE 10: Veterans Rand 12 Item Health Survey: [*Component scale here*] at Baseline, by Medical Center and Treatment

Center	OVH						EVH						Total					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Albuquerque (501)																		
Boston (523)																		
Cleveland (541)																		
Miami (546)																		
Durham (558)																		
Gainesville (573)																		
Houston (580)																		
Minneapolis (618)																		
New York (630)																		
Asheville (637)																		
Pittsburgh (646)																		
Portland (648)																		
San Francisco (662)																		
Tampa (673)																		
Tucson (678)																		
Milwaukee (695)																		
Total																		

TABLE 11: Conversion to Open Harvest Procedure, by Medical Center and Harvester, in Patients Randomized to Endoscopic Harvest Procedure.

Center	Harvester	Conversion		Randomized
		N	%	N
Albuquerque (501)	01			
	Total			
Boston (523)	01			
	02			
	Total			
Cleveland (541)	01			
	Total			
Miami (546)	01			
	02			
	03			
	Total			
Durham (558)	01			
	02			
	03			
	Total			
Gainesville (573)	01			
	02			
	Total			
Houston (580)	01			
	02			
	03			
	Total			
Minneapolis (618)	01			
	02			
	Total			
New York (630)	01			
	Total			

Asheville (637)	01			
	02			
	Total			
Pittsburgh (646)	01			
	Total			
Portland (648)	01			
	02			
	03			
	Total			
San Francisco (662)	01			
	02			
	Total			
Tampa (673)	01			
	02			
	Total			
Tucson (678)	02			
	Total			
Milwaukee (695)	03			
	04			
	05			
	Total			
Total	**Total**			

TABLE 12: Reasons for Conversion to Open Harvest Procedure, by Medical Center

Center	Bleeding	Injury to SVG	Unacceptable EVH procedure time	Insufficient amount of usable vein	Unanticipated graft needed	Harvester unable to locate vein	Other	Total
Albuquerque (501)								
Boston (523)								
Cleveland (541)								
Miami (546)								
Durham (558)								
Gainesville (573)								
Houston (580)								
Minneapolis (618)								
New York (630)								
Asheville (637)								
Pittsburgh (646)								
Portland (648)								
San Francisco (662)								
Tampa (673)								
Tucson (678)								
Milwaukee (695)								
Total								

TABLE 13: Conversion to Open Harvest Procedure, by Medical Center and Harvester, Excluding Conversions Completed Because Unanticipated Graft Required Additional Vein, in Patients Randomized to Endoscopic Harvest Procedure.

		Conversion		Randomized
Center	**Harvester**	**N**	**%**	**N**
Albuquerque (501)	01			
	Total			
Boston (523)	01			
	02			
	Total			
Cleveland (541)	01			
	Total			
Miami (546)	01			
	02			
	03			
	Total			
Durham (558)	01			
	02			
	03			
	Total			
Gainesville (573)	01			
	02			
	Total			
Houston (580)	01			
	02			
	03			
	Total			
Minneapolis (618)	01			
	02			
	Total			
New York (630)	01			

	Total			
Asheville (637)	01			
	02			
	Total			
Pittsburgh (646)	01			
	Total			
Portland (648)	01			
	02			
	03			
	Total			
San Francisco (662)	01			
	02			
	Total			
Tampa (673)	01			
	02			
	Total			
Tucson (678)	02			
	Total			
Milwaukee (695)	03			
	04			
	05			
	Total			
Total	**Total**			

TABLE 14: Mean [SYNTAX Score, VASQIP Patient Risk Calculation, STS Risk of Mortality], Total and by Medical Center and Treatment

Center	OVH						EVH						Total					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Albuquerque (501)																		
Boston (523)																		
Cleveland (541)																		
Miami (546)																		
Durham (558)																		
Gainesville (573)																		
Houston (580)																		
Minneapolis (618)																		
New York (630)																		
Asheville (637)																		
Pittsburgh (646)																		
Portland (648)																		
San Francisco (662)																		
Tampa (673)																		
Tucson (678)																		
Milwaukee (695)																		
Total																		

TABLE 15: Mean [SYNTAX Score, VASQIP Patient Risk Calculation, STS Risk of Mortality], by MACE and Treatment

		Yes						No					
	Harvesting Technique	**N**	**Mean**	**Std Dev**	**Median**	**Min**	**Max**	**N**	**Mean**	**Std Dev**	**Median**	**Min**	**Max**
Any MACE	OVH												
	EVH												
	Total												
Death	OVH												
	EVH												
	Total												
Myocardial Infarction	OVH												
	EVH												
	Total												
Repeat Revascularization	OVH												
	EVH												
	Total												

TABLE 16: Mean [SYNTAX Score, VASQIP Patient Risk Calculation, STS Risk of Mortality], by Age Group and Treatment

Age	OVH						EVH						Total					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
< 50 years																		
50 to 59 years																		
60 to 69 years																		
70 to 79 years																		
> 79 years																		
Total																		

TABLE 17: Mean [SYNTAX Score, VASQIP Patient Risk Calculation, STS Risk of Mortality], by Diabetes Status and Treatment

Diabetes	OVH						EVH						Total					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
No																		
Yes																		
Total																		

TABLE 18: Bilateral Mammary Artery Grafting, Total and by Medical Center and Treatment

	OVH				EVH				Total			
	Yes		No		Yes		No		Yes		No	
Center	N	%	N	%	N	%	N	%	N	%	N	%
Albuquerque (501)												
Boston (523)												
Cleveland (541)												
Miami (546)												
Durham (558)												
Gainesville (573)												
Houston (580)												
Minneapolis (618)												
New York (630)												
Asheville (637)												
Pittsburgh (646)												
Portland (648)												
San Francisco (662)												
Tampa (673)												
Tucson (678)												
Milwaukee (695)												
Total												

TABLE 19: Leg Incision Healing, Total and by Medical Center and Treatment

	OVH						EVH						Total					
	No Disturbance		Disturbance		Infection		No Disturbance		Disturbance		Infection		No Disturbance		Disturbance		Infection	
Center	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Albuquerque (501)																		
Boston (523)																		
Cleveland (541)																		
Miami (546)																		
Durham (558)																		
Gainesville (573)																		
Houston (580)																		
Minneapolis (618)																		
New York (630)																		
Asheville (637)																		
Pittsburgh (646)																		
Portland (648)																		
San Francisco (662)																		
Tampa (673)																		
Tucson (678)																		
Milwaukee (695)																		
Total																		

TABLE 20: Severity of Incisional Leg Pain at [Discharge, 6-weeks Postoperative], Total and by Medical Center and Treatment

Center	Harvesting Technique	Little or no impact		Some impact		Substantial impact		Severe impact		Total
		N	%	N	%	N	%	N	%	N
Albuquerque (501)	OVH									
	EVH									
	Total									
Boston (523)	OVH									
	EVH									
	Total									
Cleveland (541)	OVH									
	EVH									
	Total									
Miami (546)	OVH									
	EVH									
	Total									
Durham (558)	OVH									
	EVH									
	Total									
Gainesville (573)	OVH									
	EVH									
	Total									
Houston (580)	OVH									
	EVH									
	Total									
Minneapolis (618)	OVH									
	EVH									
	Total									
New York (630)	OVH									
	EVH									

	Total									
Asheville (637)	OVH									
	EVH									
	Total									
Pittsburgh (646)	OVH									
	EVH									
	Total									
Portland (648)	OVH									
	EVH									
	Total									
San Francisco (662)	OVH									
	EVH									
	Total									
Tampa (673)	OVH									
	EVH									
	Total									
Tucson (678)	OVH									
	EVH									
	Total									
Milwaukee (695)	OVH									
	EVH									
	Total									
Total	OVH									
	EVH									
	Total									

TABLE 21: Major Adverse Cardiac Events, Overall and by Treatment

Center	Harvesting Technique	Yes		No		Total	
		N	%	N	%	N	%
Any Major Adverse Cardiac Event	OVH						
	EVH						
	Total						
Death	OVH						
	EVH						
	Total						
Myocardial Infarction	OVH						
	EVH						
	Total						
Repeat Revascularization	OVH						
	EVH						
	Total						

TABLE 22: Mean Length of Follow-up in Days, by Medical Center and Treatment

Center	OVH						EVH						Total					
	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max	N	Mean	Std Dev	Median	Min	Max
Albuquerque (501)																		
Boston (523)																		
Cleveland (541)																		
Miami (546)																		
Durham (558)																		
Gainesville (573)																		
Houston (580)																		
Minneapolis (618)																		
New York (630)																		
Asheville (637)																		
Pittsburgh (646)																		
Portland (648)																		
San Francisco (662)																		
Tampa (673)																		
Tucson (678)																		
Milwaukee (695)																		
Total																		

TABLE 23: Cumulative Serious Adverse Event Incidence using MedDRA coding in Randomized Participants, by Body System and Preferred Term

	OVH				EVH				Total			
Body System and Preferred Terms	Participants		Events		Participants		Events		Participants		Events	
	N	%	N	%	N	%	N	%	N	%	N	%
Cardiac Disorders												
Cardiac failure congestive												
…and so on												

TABLE 24: Protocol Non-compliance

Center	Rate of Reporting	Participant ID	Protocol Non-Compliance Code	Date of Deviation
Albuquerque (501)				
…				
… and so on				

FIGURE 2: Kaplan-Meier Survival Curves

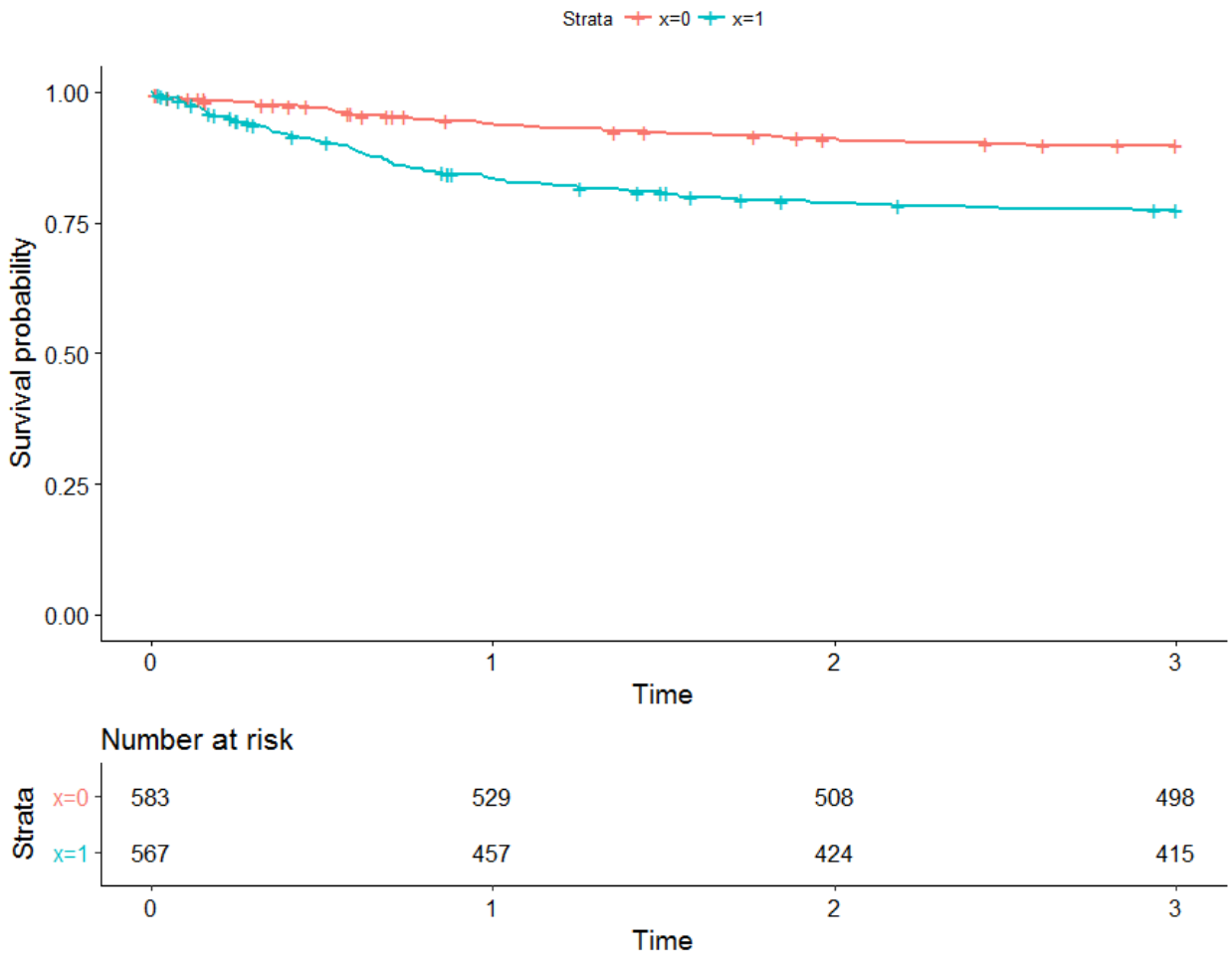

TABLE 25: MACE, Active Follow-up: Results of Multivariable Cox Proportional Hazards Regression Model

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square Test Statistic	p-value	Hazard Ratio	95% Hazard CI
EVH (vs. OVH)							
Covariate 1							
…							
… and so on							

TABLE 26: Major Adverse Cardiac Events at 1-year and 3-year, by Treatment

		OVH		EVH		Total		
		N	%	N	%	N	%	p-value
1-Year	**MACE**							
	Death							----
	MI							----
	RR							----
3-Year	**MACE**							
	Death							----
	MI							----
	RR							----

TABLE 27: Leg Incision Healing by Treatment

	OVH		EVH		Total		
	N	%	N	%	N	%	p-value
No Disturbance							----
Complication (Any Disturbance)							

TABLE 28: Leg Incision Healing by Treatment: Results of Multivariable Logistic Regression Model

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square Test Statistic	p-value	Odds Ratio	95% CI
EVH (vs. OVH)							
Covariate 1							
…							
… and so on							

TABLE 29: Seattle Angina Questionnaire: Change from Baseline by Treatment

			OVH		EVH		Total		
			N	%	N	%	N	%	p-value
[Component scale]	6-week	Improved							
		No Change							----
		Worsened							-----
	12-month	Improved							
		No Change							----
		Worsened							-----

* No change = (mean score change < 5)

TABLE 30: Seattle Angina Questionnaire: Results of ANCOVA Model

		Parameter	DF	Parameter Estimate	Standard Error	t-Test Statistic	p-value
[Component scale]	*[6-week /12-month]*	Intercept					
		Baseline Score					
		EVH (vs. OVH)					
		Interaction (if needed)					

TABLE 31: Impact and Severity of Incisional Leg Pain at by Treatment

		OVH		EVH		Total		
		N	%	N	%	N	%	p-value
Discharge	**Little or no impact** (impact score ≤ 50)							
	Some impact (50 < impact score ≤ 57)							----
	Substantial impact (57 < impact score ≤ 63)							-----
	Severe impact (impact score > 63)							----
	Severe (per severity rating) (Score of 3 or above)							
6-Weeks	**Little or no impact** (impact score ≤ 50)							
	Some impact (50 < impact score ≤ 57)							----
	Substantial impact (57 < impact score ≤ 63)							-----
	Severe impact (impact score > 63)							----
	Severe (per severity rating) (Score of 3 or above)							

TABLE 32: Veterans Rand 12 Item Health Survey: [*Component scale here*] by Medical Center and Treatment

	OVH						EVH						Total						p-value
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	
Baseline																			
6 weeks																			
12 months																			
6-week change																			
12-month change																			