Vest Prevention of Early Sudden Death Trial: Prevention of Sudden Death After Myocardial Infarction Using a LifeVest Wearable Cardioverter-defibrillator (Formerly VEST/PREDICTS)

NCT01446965

Document Date: March 2, 2017

VEST & VEST REGISTRY PROTOCOL

SUMMARY OF REVISIONS up to V3.2

Version 1.0 to Version 1.1 (12/10/08)

1. Exclusion criterion for chest circumference changed from specific measurement to "Chest circumference too small or too large for LifeVest garment.

Version 1.1 to Version 1.2 (2/2/2009)

1. In the previous modification we changed the wording of the chest dimension exclusion criterion to "too small to too large for LifeVest garment" and added a footnote that included chest size up to 66 inches based on a recommendation of a representative of the manufacturer. The manufacturer now advises us that the footnote should be changed back to the 'official' upper limit of 56-inchesas changed in Table 1-1 on page 7.
2. We have changed the wording to be consistent with the enrollment window of 7-days post-discharge so that enrollment activities are not all said to occur in the hospital:
    a. Top of Page 7 first paragraph, deleted 'prior to discharge'.
    b. Middle of page 8, 'Occurs' replaced with 'Begins', 'will' replaced with 'may'.
3. Table 1-2 we changed wording to clarify that
    a. baseline testing may occur in hospital or clinic,
    b. ECG and EF (ejection fraction measurement are abstracted from admission records, and
    c. ECG and SAECG are measurements comprise one testing procedure ,
4. On page 15, Section 1.5.7, bottom of 2nd paragraph we clarify that the compliance reports are not printed and sent, but accessed via the VP study website.

Version 1.2 to Version 1.3 (4/22/2009)

1. Page 1-7: Table 1-1
    a. Inclusion criteria #2 , measurement interval for ejection fraction changed to 8 hours after MI and 8 hours after a PCI.
    b. Exclusion criteria removed: Patients who have undergone CABG or other surgery within 30 days of screening
2. Page 1-9 : Table 1-2
    a. Correction of typographical error to insert V7 (previously skipped in error) and subsequent visit numbers.
    b. Elimination of risk stratification testing at Visit 6 (Year2) including ECG/SAECG, Exercise Testing (TWA), 24° Holter and 6MW, BRS, and Local Labs
3. Page 1-10:
    a. Narrative changed to remove all references to risk stratification testing during Year 2.
    b. All pages footnote: Version change from 1.2 to 1.3; and footnote date change to 4-22-09

Version 1.3 to Version 1.3a (4/22/2009-*same date as above*)

In April 2009, the CHR approved a minor modification that included the elimination of the third round of risk stratification testing at the 2-year visit (as had been suggested by the VEST/PREDICTS Executive Committee). However, during the May 12th meeting of the VEST/PREDICTS Steering Committee, the members voted to reinstate the third round of risk stratification testing.

1. Page 1.7: Table 1-1
2. Reinstatement of risk stratification testing at Visit 6 (Year2) including ECG/SAECG, Exercise Testing (TWA), 24° Holter and 6MW, BRS, and Local Labs
3. Page 1.10: Narrative changed to reinstate all references to risk stratification testing during Year 2.
4. All pages footnote: Version change from 1.3 to 1.3a; and date change to 5-22-09.

Version 1.3 and 1.3a to Version 2.0 (6/24/2009)

Enrollment into the VEST/PREDICTS study was significantly lower than expected. Consequently, during meetings in May/June of 2009, the VEST/PREDICTS NIH-appointed Data Safety and Monitoring Board, Steering Committee, and Executive Committee members voted to approve three study modifications that include, 1) allowing separate entry into the VEST only or PREDICTS only components of the study while retaining participation into the combined VEST/PREDICTS study, 2) a reduction in the sample size for PREDICTS to 2400, and 3) an increase in the number of clinical sites implementing our protocol from 60 to 90.

1. Relevant changes to the Protocol can be found on pages 1-7 to pages 1-10 where we present two tables and accompanying narrative summarizing different inclusion and exclusion criteria for the three entry options. The inclusion and exclusion criteria for 'VEST/PREDICTS combined' and 'VEST only' participation are the same, and have not changed from the most recent approved protocol version 1.3a. (as displayed in Table 1-1a on page 1-7).
2. The modified inclusion and exclusion criteria for 'PREDICTS only' are displayed in Table 1-1b on page 1-8. For participants enrolling in PREDICTS only, we broadened the inclusion criteria to include patients ≤6 months from an MI (#1, Table 1-1b). Therefore the qualifying ejection fraction (EF) is either measured during the MI hospitalization, or if the patient presents outside of the 7-day post discharge window, the "most recent EF" before enrollment is the qualifying EF (#2, Table 1-1b). This change allows for a larger pool of patients and parallels what is done in practice through application of current ICD implantation guidelines.
3. The modified exclusion criteria for 'PREDICTS only' excludes patients with an existing ICD, with a previous cardiac arrest, and with sustained ventricular tachycardia or ventricular fibrillation. However, patients are not excluded who have had prior CABG (after qualifying MI), paralleling current guidelines (3 months after CABG).
4. Page 10:Table 1-2 has been modified to reflect different tests, visits, and data collected based on the three enrollment options.
5. Page 14: The ICD or Reveal Implantation section was changed to allow for enrollment timing options in PREDICTS only.
6. Page 21-22: The bottom paragraph on page 21 and top paragraph on page 22 were modified to reflect the reduction in sample size for PREDICTS and the concurrent changes in the analysis plan.

Version 2.0 to Version 2.1 (1/29/2010)

On December 3, 2009, VEST/PREDICTS (VP) Executive and Steering Committees and the NIH appointed DSMB approved a plan to 1) change the primary outcome in VEST from all-cause mortality to sudden death and, 2) extend the follow-up time in VEST to 3 months. These changes will allow VEST to be completed with a sample size of 1900 instead of the original target of 4506, and still provide valuable information on the effectiveness of a wearable defibrillator on reducing sudden death in the post MI period.
Because this change in endpoint constitutes a departure from that which was originally reviewed, the NHLBI decided to discontinue support for VEST (they will continue support for PREDICTS) and ZOLL has agreed to provide sole support for the continuation of VEST with the above changes. The Protocol has been modified as follows:

1. Protocol Version change from 2.0 to 2.1
2. VEST Primary outcome changed from all-cause mortality to sudden death mortality
3. VEST follow-up changed from 2 months to 3 months
4. VEST sample size changed from 4506 to 1890 (1900)
5. Changes in sample size calculations methodology for VEST
6. Changes in Organization and Administration (reflecting NHLBI decision)
7. DSMB membership list removed

Version 2.1 to Version 3.0 (9/27/2011)

As of March 1, 2010 enrollment in the PREDICTS arm of the study was stopped due to the withdrawal of funding from the NHLBI followed by the withdrawal of funding from Medtronic. After these decisions, ZOLL Lifecor Corporation decided to increase the amount of funding originally proposed to allow the Coordinating Centers to complete the VEST arm of the study and add a VEST Registry. Subsequently, the protocol was revised to reflect the needs of the VEST and VEST Registry. The changes were reviewed and accepted by the DSMB on September 27, 2011 and on November 11, 2011, UCSF's Committee on Human Research also approved the changes to the protocol as well as the consent forms

The two major changes are as follows: 1) As of July 2011, the PREDICTS study follow-up is completed. Therefore, all PREDICTS-related text has been removed from the proposed new version of the protocol and 2) As suggested

by the DSMB, the primary outcome was changed from sudden death mortality to sudden death and death due to ventricular arrhythmia. All references to the primary outcome have been revised, including Specific Aim 1.
The protocol has been revised with the following changes:

1. Protocol Version change from 2.1 to 3.0
2. Page 3: Addition of VEST Registry
3. Page 4: Addition of Aim 2: "To create a registry of VEST eligible patients for long-term follow-up to determine health and utilization outcomes. All VEST eligible patients will be offered participation in the VEST registry including those who previously participated in VEST."
4. Page 4: Stephen B. Hulley, MD, MPH has retired and the new DCC PI is Mark J. Pletcher MD MPH
5. Page 5: Table 1 revised inclusion criteria to allow for patients with planned CABG and exclusions related to PREDICTS removed.
6. Page 6: Visits related to PREDICTS were removed (e.g., 2-6 month testing, post-implantation visits. A 1-year visit was added to collect VEST registry data.
7. Pages 8-9: Previously, stratification was conducted by revascularization status (PCI/No PCI). With the change in inclusion criteria for CABG, stratification will now be by "revascularization status (i.e., None/PCI/CABG)".
8. Page 11: Table 3, outcomes related to PREDICTS were removed
9. Page 12: Additional detail was added to the VEST analysis plan.
10. Page 13: Revisions were made to the plan for "Updating Sample Size":
11. Page 14: Biological specimens will no longer be collected, as this was PREDICTS-related.
12. Page 14: Addition of VEST Registry in order to determine long-term outcomes in patients who are eligible for VEST, including those who enroll and complete the trial and those have previously participated in VEST. All patients in the VEST Registry will have yearly follow-ups to determine their vital status, their most recent EF, whether an ICD has been implanted and whether they have had any cardiovascular hospitalizations/events. These will be obtained by searching medical records and death indexes, and by interviewing participants by phone.
13. Page 15: DCC now led by Mark Pletcher.
14. Page 15: Reference to all previous industry partners except ZOLL removed
15. Page 16: Reference to all previous industry partners except ZOLL removed
16. Page 17: References to Medtronic removed

Version 3.0 to Version 3.1 (12/20/2011)

Administrative revisions:

1. Protocol Version change from 3.0 to 3.1
2. Page 3: Changes to Objective #2: To create a registry of VEST eligible patients for long-term follow-up to determine health and utilization outcomes. All VEST eligible patients study participants will be offered participation in the VEST registry including those who previously participated in VEST.
3. Page 4 Changes to Specific AIM # 2: To create a registry of VEST eligible patients for long-term follow-up to determine health and utilization outcomes. All VEST study participants will be offered participation in the VEST registry including those who previously participated in VEST.
4. Page 4: Removal of Jeff Olgin's title "and Chief of the Cardiac Electrophysiology and Arrhythmia Service"
5. Page 5, Table 1: Exclusion Criteria #5: "institution setting" changed to "skilled nursing facility"
6. Page 6, Table 2: Test Reports, 12 Lead ECG and Local Labs: changed to V0 Enrollment only
7. Page 6 Table 2: Test Reports, Echocardiography: changed to V0, V2 and Registry
8. Page 7, Revisions made: VEST Registry Follow-up Telephone Call: Participants will be contacted by phone at least yearly to gather follow-up data. Participants will be asked about changes in medication, intervening hospitalizations, and simple follow-up questions regarding ICD/pacemaker device implantation.
9. Page 7, Section 1.5.5 Interventions in VEST, Revisions made: Participants randomized to the LifeVest will be fit with the LifeVest ideally before they are discharged from the hospital or clinic, but the fitting may occur at the participant's home within 7 days post discharge from the index MI.
10. Page 9, Section 1.5.6 Randomization, Revisions made: Dr. Eric Vittinghoff replaced with "the Senior Statistician"
11. Page 10, Outcome Adjudication: Dr. Joel Simon removed
12. Page 13, Removal of: "These rules are in accord with guidelines suggested by Gould."
13. Page 13, Section 1.7 VEST REGISTRY, Revisions made: In order to determine long-term outcomes in patients who are eligible and enroll to participate in VEST, all patients in the VEST Registry will have at least yearly follow-up to determine vital status, most recent EF, whether an ICD has been implanted and whether they have had any cardiovascular hospitalizations/events.
14. Page 15, Data Transmissions from Reading Centers, Laboratories, Removal of: "or ICD, or from a test producing digital data such as an echocardiogram, ECG, or Holter monitor"

15. Appendix 1.B Steering Committee: Removal of old members and additions of new members including changes to titles
16. Appendix 1.C Predictor Measures (selected): Removal of this appendix

Version 3.1 to Version 3.2 (June 8, 2016)

In October 2015, the VEST Data and Safety Monitoring Board (DSMB) reviewed the sample size re-estimation calculations after 1500 participants completed their Month 3 follow-up. The blinded interim analysis revealed that average LifeVest wear time was below target (i.e., below the estimated avg. of 17 hours per day, which was used for the original sample size calculations), but the composite event rate had been on target throughout the study. Due to the lower LifeVest average wear-time, which decreased the study's current estimated power, the DSMB was concerned about a substantial likelihood of type II error.

In March 2016, the DSMB recommended that the VEST sample size be increased by at least an additional 400 participants, in order to maintain adequate study power. The DSMB also recommended that VEST study investigators and staff continue intense efforts to maintain or increase the recent improvement in wear-time rates, which is also essential to achieve adequate power.

In April 2016, ZOLL agreed to provide support for the recommended increase of 400 participants and the VEST Steering Committee approved this amendment to the protocol on April 25, 2016.

At the end of the trial, we will perform a National Death Index search for U.S. participants with unknown vital status to obtain data on the primary (Sudden death) and secondary (all cause mortality) study outcomes. Confirmation of VEST participant deaths is of vital importance, in order to reduce the risk of missing data bias which may impact the robustness of the final trial results.

The Protocol has been modified with the following changes:

1. Cover Page: Protocol Version Change to 3.2, Date change to June 8, 2016
2. Cover Page: More Steering Committee Dates, DSMB Meeting Dates, and UCSF CHR approval dates added
3. Page 6, Section 1.5.3 Recruitment Plan: The original sample size calculation estimated that 1900 participants would be enrolled in VEST (see Sample Size Calculations, below). Per protocol, an interim blinded sample size analysis was performed when 1,000 and 1,500 participants were enrolled, respectively. Per protocol, these analyses demonstrated the need to increase the sample size (see Appendix A). Therefore, approximately 2300 participants will be enrolled in VEST (see Sample Size Calculations, below).
4. Page 13, Section 1.5.12 Sample Size Calculations: Added text regarding Final sample size, DSMB recommendations, and Steering Committee approval.
5. Page 13, Section 1.7.1 National Death Index Search at End of Trial: added aforementioned text
6. Page 22, Reference: International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials [E9]. 5 February 1998.
7. Page 24, Appendix 1.b Steering Committee – removal of one Site PI

Vest prevention of Early Sudden death Trial (VEST)
and
VEST Registry

PROTOCOL

Version 3.2

June 8, 2016

Clinical Coordinating Center (CCC)
Department of Medicine, University of California, San Francisco

Data Coordinating Center (DCC)
Department of Epidemiology and Biostatistics, University of California, San Francisco

FUNDERS
ZOLL, A108523 (VEST)

Approvals
☒ Executive Committee (Date 10/15/07, 4/7/09, 5/12/09, 11/19/09, 8/31/11)
☒ Steering Committee (Date 11/12/07, 5/12/09, 11/20/09, 5/13/10, 10/29/10, 4/25/2016)
☒ DSMB (Date 1/3/08, 9/8/2008, 2/2/09, 3/16/09, 12/3/09, 6/1/10, 11/29/10, 9/27/11, 5/14/2012, 10/30/2013, 3/14/2014 2/6/2015)
☒ UCSF CHR/IRB (Initial Approval 6/28/07; Amendments approved 1/24/08, 2/24/08, 12/24/2008, 2/2/09, 4/22/09, 6/26/09, 8/10/09, 2/10/2010; 3/3/2011; 3/6/2011; 3/21/2011; 7/14/2011, 11/11/2011, 11/29/2011, 7/12/2012, 7/11/2013, 7/23/2014, 7/2/2015)

Table of Contents

Protocol Summary

Objective
To conduct a multicenter, randomized controlled trial to test the hypothesis that a non-invasive wearable cardioverter defibrillator (WCD) will reduce sudden death and death due to ventricular arrhythmia in the first 90 days following an MI in participants with left ventricular dysfunction (EF≤35%).

To create a registry of VEST eligible patients for long-term follow-up to determine health and utilization outcomes. All VEST eligible patients study participants will be offered participation in the VEST registry including those who previously participated in VEST.

Study Population
Participants hospitalized with an MI with left ventricular ejection fraction (LVEF) of ≤35% who are at least 18 years old.

Study Design
Randomized clinical trial

Interventions
LifeVest + Optimal post-MI/CHF treatment ***vs.*** Optimal post-MI/CHF treatment only
(2/3 of participants will be randomized to receive the LifeVest)

Primary Outcomes
Sudden death and death due to ventricular arrhythmia

Secondary Outcomes
Non-sudden death mortality
Cardiovascular mortality
Total mortality
Arrhythmic Death
Non-Sudden Fatal MI
Congestive Heart Failure Death
Other Cardiac Death
Stroke Death
Other Non-Cardiac Death
Indeterminate Cause of Death
Non-Fatal MI
Non-Fatal Congestive heart failure
Non-Fatal Stroke/Transient Ischemic Attack
Non-Fatal Atrial Fibrillation
Inappropriate Shock – SVT
Inappropriate Shock-malfunction
Inappropriate Shock-oversensing
Adverse Events
Vest Compliance
Quality of Life
Resource Utilization/Cost
Eventual ICD implantation (VEST registry)
Change in EF (VEST registry)
Mortality (VEST registry)
CV hospitalizations (VEST registry)

Study Duration
90 days for the intervention trial (VEST)
Long-term post-intervention follow-up (VEST registry)

PART 1. DESIGN

1.1 SPECIFIC AIMS

1. To conduct a multicenter, randomized controlled trial to test the hypothesis that a non-invasive wearable automatic defibrillator vest will reduce sudden death and death due to ventricular arrhythmia without a concomitant increase in non-sudden death mortality in the first 90 days following an MI in participants with left ventricular dysfunction (EF≤35%). This is the Vest prevention of Early Sudden death Trial (VEST). Participants will be randomized in a 2:1 fashion to receive optimal post-MI and CHF medical therapy plus a wearable defibrillator vest, or optimal post-MI and CHF medical therapy alone at the time of hospital discharge.

2. To create a registry of VEST eligible patients for long-term follow-up to determine health and utilization outcomes. All VEST eligible patients will be offered participation in the VEST registry including those who previously participated in VEST.

1.2 BACKGROUND

While implantable cardioverter-defibrillators (ICDs) have had some impact in reducing the nearly 500,000 annual sudden cardiac deaths (SCD) in the US[2], our current treatment strategy is still limited. Recent studies have demonstrated a very high rate of sudden cardiac death in the first several months following a myocardial infarction (MI), particularly in participants with depressed left ventricular function. One study (DINAMIT) showed that implanting an ICD during this period reduced arrhythmic mortality, but did not reduce overall mortality.[3] There are several potential reasons this study was negative including the possibility that the actual implant, anesthesia and DFT testing in the early post-MI period could adversely affect remodeling. Another possibility is that this was a select population of patients with low heart rate variability and thus more prone to a non-arrhythmic death. Nonetheless, because no study to date has demonstrated a mortality benefit of implanting an ICD within 40 days immediately after MI, the current practice is to wait at least 40 days after an MI. This leaves an unprotected, vulnerable period of increased sudden death risk prior to ICD implantation. VEST is designed to assess a potential strategy aimed at decreasing the high sudden death rate in this early post-MI period.

1.3 PROTOCOL PRINCIPALS

Jeffrey Olgin MD, Principal Investigator, Clinical Coordinating Center (CCC), Professor of Medicine and Chief of the Division of Cardiology, University of California, San Francisco (UCSF)

Byron Lee MD, MAS, Co-Investigator, CCC, Associate Professor of Medicine in the Division of Cardiology and Attending Physician in the Cardiac Electrophysiology and Arrhythmia Service, UCSF

Mark J. Pletcher, MD, MPH, Principal Investigator, Data Coordinating Center (DCC), Associate Professor of Epidemiology and Biostatistics, UCSF

1.4 ETHICAL CONSIDERATIONS

The study was peer-reviewed by the NIH and a grant was awarded that funded the first 3 years of the study. NIH funding ended in 2010. The UCSF Committee on Human Research has approved the study protocol and model consent form (Approval Number H43109-30941-01). The protocol has also been approved by the Steering Committee and the DSMB. Prior to initiation of recruitment of study participants, the study protocol and consent form as well as other important study documents will be reviewed and approved by the Institutional Review Boards of all participating clinical sites. Sites will be encouraged to use the study consent template unchanged, but we recognize that some IRBs may have varying requirements and the CCC will work with sites to ensure IRB approval of the study protocol and consent form. The CCC will ensure that all sites have up-to-date IRB approval, will track when sites are due for renewal and ensure that no enrollment occurs during any lapses in IRB approvals.

1.5 DESIGN AND METHODS

1.5.1 Overview

VEST is a randomized, controlled trial to determine whether a wearable defibrillator vest (LifeVest, ZOLL, Pittsburgh, PA) reduces sudden death and death due to ventricular arrhythmia in the first 90 days following an MI. We hypothesize that a completely non-invasive, wearable defibrillator will decrease sudden death and death due to ventricular arrhythmia by decreasing arrhythmic mortality without an increase in non-arrhythmic mortality.

The study timelines are shown in Figure 1. Participants hospitalized for an acute MI who meet the inclusion and exclusion criteria will be enrolled. They will then be randomized either to vest or no vest in a 2:1 fashion. Both groups will receive optimal post-MI and CHF medical therapy for their condition.

Table 1. VEST inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Patients identified in the hospital or within ***7 days*** after discharge with a diagnosis of an acute MI (STEMI or Non-STEMI)[1] 2. LV ejection fraction ≤35%, determined at the following time point: a) if no PCI within the first 8 hours following the MI: **≥8° after MI** **b)** if acute PCI occurs within 8° of MI: **≥8° after PCI** c) if CABG is planned (before or within 7 days of discharge), wait to enroll and then use the **most recent assessment at least 48° post CABG**. 3. Age ≥18 years	1. Existing ICD or indication for an ICD at the time of screening 2. Existing unipolar pacemakers/leads 3. Chronic renal failure requiring hemodialysis after hospital discharge 4. Chest circumference too small or too large for LifeVest garment* 5. Participants discharged to a skilled nursing facility with an anticipated stay > 7 days 6. Pregnancy 7. Inability to consent 8. Any other condition or circumstance that in the judgment of the clinician makes the participant unsuitable for the study

**as of this writing, garments are available for chest circumference of 26-56 inches.*

1.5.2 Study Participants

Participants hospitalized with an MI (or discharged after a recent MI) will be approached and evaluated for enrollment in the study. A standard definition of acute MI based on recently published criteria will be used:[1]

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the upper limit of normal (ULN) for the particular lab, together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia (new ST-T changes) or new left bundle branch block (LBBB);
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above 3 x ULN for your lab in the setting of a percutaneous coronary intervention (PCI).

Those who meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for randomization in VEST. Table 1 lists the specific inclusion and exclusion criteria for VEST.

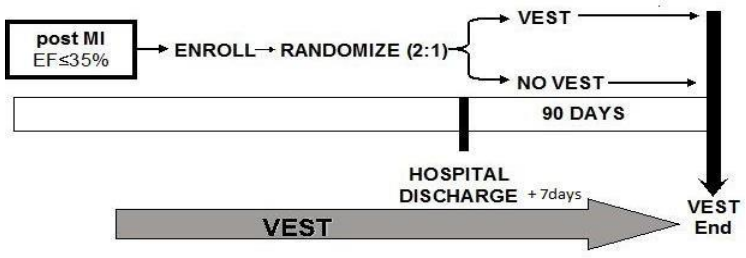


Figure 1. Overview of study timeline

1.5.3 Recruitment Plan

The original sample size calculation estimated that 1900 participants would be enrolled in VEST (see Sample Size Calculations, below). Per protocol, an interim blinded sample size analysis was performed when 1,000 and 1,500 participants were enrolled, respectively. Per protocol, these analyses demonstrated the need to increase the sample size (see Appendix A). Therefore, approximately 2300 participants will be enrolled in VEST (see Sample Size Calculations, below). Sites will be chosen based on their success in other similar trials and access to adequate MI patient volumes.

The CCC will oversee the recruitment effort and ensure that clinical sites actively recruit as many participants as possible. The CCC Project Director will act as a recruitment liaison with the sites, monitoring recruitment goals at each site and facilitating information sharing about successful recruitment strategies. If a center is found to be recruiting below goals, the CCC will arrange for those sites to exchange ideas and recruitment strategies with successful clinics, followed if appropriate by a site visit to assist the clinic in correcting any problems. Sites with continued recruitment difficulties may be closed before study termination.

1.5.4 Schedule and Description of Participant Visits

Each of the study participants will be first seen in the hospital during their admission for MI or after discharge in the clinic within the window of enrollment. They will then be followed with one phone call and one clinic visit. The schedule for testing and data collection is outlined in Table 2. The visit timeline and windows for visits are provided in Chapter 3 of the Operations Manual.

Table 2: Scheduled visits and data collection

DATA COLLECTED AND TESTING PERFORMED	VISITS			
		Post-discharge		
	V0	V1	V2	*Registry*
	Enrollment	1 Month Phone	3 Month Visit	
Screening and Medical History	X			
Vital signs, discharge meds & diagnoses (from chart)	X			
Symptom Checklist		X	X	
Medication Review	X	X	X	
Medical Care Utilization		X	X	X
Vital Status			X	X
QOL Survey			X	
Test Reports • 12 lead ECG • Local Labs	From Medical Record			
• Echocardiography	From Medical Record		From Medical Record	From Medical Record
Home Monitoring ▪ LifeVest	upload baseline at fitting	**3 times in 1st week, then weekly**		

- *Enrollment Visit (V0):* Begins during the participant's hospitalization for MI or within the window of enrollment after discharge. Participants who meet enrollment criteria will be asked to participate in the study after they are medically stable. After consent for VEST, they will be enrolled and randomized to vest or no vest. If randomized to vest, they may leave the hospital with the vest. The enrollment visit will involve collection of information and data abstracted from the hospital chart.
- *1 Month Follow-up Telephone Call (V1)*: All participants will be contacted by phone to gather follow-up data. Participants will be asked about changes in medication, intervening hospitalization or visits to the emergency department, any problems with the vest (if randomized to the LifeVest) and a simple symptom checklist.
- *3 Month Visit (V2):* All participants will be seen for clinical data collection/final visit. Participants will be asked about changes in medication, intervening hospitalization or visits to the emergency department, any problems with the vest (if randomized to the LifeVest), and a simple symptom checklist. The patient's most recent EF will be extracted from his/her medical record and assessment of qualification for primary prevention ICD will also be recorded. A Quality of Life survey will be

mailed to the participant prior to this visit for self-administration and returned to the clinical site during this visit.

- *VEST Registry Follow-up Telephone Call:* Participants will be contacted by phone at least yearly to gather follow-up data. Participants will be asked about changes in medication, intervening hospitalizations, and simple follow-up questions regarding ICD/pacemaker device implantation.

Continuous Participant Monitoring (during the study period: V0-V2)

In addition to the visits described above, participants randomized to LifeVest will have continuous remote monitoring via the LifeVest.

Monitoring Capabilities and Data Collection from LifeVest: The LifeVest performs constant ECG monitoring while it is worn. It records all ventricular tachyarrhythmias that last more than 15 seconds and asystolic events (<20 beats per minute). Bradyarrhythmias (<40 bpm) are logged but no ECG is recorded. It also compiles compliance data by recording the amount of the time the LifeVest is worn each day. This data will be uploaded via modem and phone line. After initial setup, the coordinator or fitter (from ZOLL Lifecor) will upload the participant's baseline data, then the participant will upload (from home) every other day for a total of 3 times during the first week and then subsequently on a weekly basis. The DCC will notify enrolling sites if participants are not sending scheduled transmissions. The enrolling sites can then contact participants to discover problems and encourage compliance. Sites with persistent or numerous poorly compliant participants will be visited and their staff re-trained.

The participant's compliance to the visit schedule will be continuously monitored on the study website by clinical site. The CCC will review visit compliance reports with the clinical sites on the Quality Control Committee conference calls/meetings to identify problems and recommend corrective action. If a participant misses a scheduled visit, clinic staff will contact him/her immediately to review the reasons for the missed visit, to identify any barriers that can be corrected, and to reschedule the visit.

1.5.5 Interventions in VEST

Participants will be randomized in a 2:1 fashion to either receive optimal post-MI and CHF medical therapy plus a wearable defibrillator (LifeVest) or optimal post-MI and CHF medical therapy alone for 90 days. Participants randomized to the LifeVest will be fit with the LifeVest ideally before they are discharged from the hospital or clinic, but the fitting may occur at the participant's home within 7 days post discharge from index MI.

Compliance: Prior to consent to participate in the study, potential participants may be shown the LifeVest and given an opportunity to try it on. Participants will be told that they will be expected to wear the LifeVest for at least 23 hours a day for 3 months. Site coordinators will be trained on how to use the LifeVest and will help teach participants how to use the LifeVest properly to enhance compliance. Participants will be fully trained on how to put the LifeVest on and off, and how to temporarily disable the LifeVest by pushing a button to prevent inappropriate or premature shock. Additionally, participants will be trained how to maintain the LifeVest and determine if it is functioning normally as well as how to transmit data from the LifeVest monitor via the integrated modem over a phone line. Participants, regardless of group assignment, will receive optimal medical therapy based on current AHA/ACC Guidelines unless there is a contraindication[7, 8].

Participants will be urged to wear the LifeVest continuously after hospital discharge for at least 3 months (or until ICD implantation). They will be instructed to take the LifeVest off only for bathing or showering. Participants will send data from the LifeVest monitor via modem 3 times a week for the first week and on a weekly basis thereafter. These data will include the compliance of wearing the LifeVest, Holter data, arrhythmia occurrence and shocks (delivered and aborted). Site coordinators will contact participants who don't transmit on schedule or who wear the LifeVest <20 hours per day for 2

consecutive days by phone to discuss any problems participants might be experiencing with the purpose of obtaining excellent overall compliance rates. For sites with poor compliance rates, the following remedial actions will be taken: 1) discussions with site coordinator; 2) engagement of ZOLL Lifecor staff and site visit for coordinator training, if needed; 3) engagement of ZOLL Lifecor staff for fitting of participants.

Blinding to treatment assignment: Participants and clinicians will not be blinded to treatment assignment (LifeVest versus no LifeVest). Since the primary outcome in *VEST* is sudden death and death due to ventricular arrhythmia, it is unlikely that this outcome would be significantly affected by either participant or clinician knowledge of treatment assignment.

Blinding to arrhythmias: Clinicians will be blinded to most arrhythmia recordings from the LifeVest in the group assigned to wear the LifeVest. This is necessary to prevent co-interventions with inappropriate anti-arrhythmic drugs or early implantation of an ICD. There are provisions for unblinding when clinically indicated, as detailed in Chapter 6 of the Operations Manual. Two types of unblinding will occur:

1) Automatic unblinding, generated by the DCC or ZOLL, which will result in electronic notification to the site and sending of LifeVest monitoring strips. Automatic unblinding will be initiated if any of the following events occurs:

- Participant receives a shock
- LifeVest alarms, but participant averts a shock or the rhythm spontaneously terminates if the rhythm lasts > 30 seconds
- Asystole or Bradycardia less than 20 bpm

2) Clinical sites can *request unblinding* and receive LifeVest strips under the following circumstances:

- Participant suffers a cardiac arrest, or reports receiving a shock or LifeVest alarm
- Participant complains of syncope or pre-syncope
- Participant complains of palpitations
- Physician deems it to be medically necessary (a protocol deviation may be reported)

The procedure for requesting these strips will require a case report form (completed by ZOLL personnel) with a diagnosis or rationale (as outlined above), the date range of strips requested and a follow-up form that documents any treatment changes resulting from viewing these strips.

Crossovers

Participants randomized to the control arm of VEST should not wear a LifeVest during the 3 month VEST follow-up period; use of a LifeVest by a control participant will be recorded as a protocol deviation.

Treatment of Participants Who Receive a LifeVest Shock

Evaluation and treatment of participants who receive a shock while wearing the LifeVest will be determined by the treating physicians. Recommendations for possible evaluation strategies and treatment will be included in the Operations Manual (Chapter Guidelines for Care of the Medical Treatment). This may include the possibility of assessing for recurrent ischemia, treatment of arrhythmias such as atrial fibrillation or titration of medication.

Early ICD Implantation

It is recognized that some participants will develop indications for ICD implantation during the 3 month VEST portion of the study. Given the short follow-up of only 3 months, we anticipate that this will be a rare event. The protocol provides for participants in the control (non-LifeVest group) and the intervention group (LifeVest group) who suffer an aborted cardiac arrest subsequent to the qualifying

MI/hospitalization to be implanted with an ICD. Participants with syncope and >30 seconds of VT may also have an ICD implant.

The following are NOT considered appropriate reasons for early ICD implantation and if elected by the treating physician will be considered protocol deviations:

- Malfunction of the LifeVest (Poor sensing or inappropriate detection/shock delivery)
- Poor participant compliance
- Non-sustained ventricular arrhythmias (<30 seconds)
- Asymptomatic ventricular arrhythmias

In addition, a detailed algorithm for initiation of anti-arrhythmic drugs for ventricular arrhythmias and atrial fibrillation based on ACC/AHA Guidelines will be provided in the operations manual.[6, 9] Deviations from these algorithms that are elected by the attending physician will be considered a protocol deviation.

1.5.6 Randomization

Participants will be randomized in a 2:1 ratio to either receive the LifeVest or not, respectively. Randomization will be stratified and blocked to protect against chance maldistribution of important predictors. Stratification will be by ejection fraction (≤25% vs. >25%) and by revascularization status (i.e., None/PCI/CABG), both known strong predictors of mortality, and by clinical site to protect against maldistribution of other unmeasured potential confounders that might be unequally distributed at different clinical sites. Randomization blocks will vary in size to protect against *predictability* of randomization assignment within clinical site/EF/revascularization strata. Block size will vary from 3 to 6, allowing for a maximum absolute deviation of 4 participants from the exact 2:1 ratio in any given site/EF/revascularization stratum. Separate tables for each stratum will be pre-generated (by existing routines developed by the Senior Statistician for the study), encrypted, and accessible only to the Senior Statistician and the DCC Data Analyst.

The DCC will implement a web-based interface that clinical sites will use to obtain randomization assignments for each enrolled participant after completion of the Enrollment Visit. Clinical sites will access the randomization website using a secure password, and will be prompted to attest that all entrance criteria are met and that informed consent has been obtained. Each inclusion and exclusion criterion will require active attestation to minimize errors of omission. Once entry criteria are verified electronically, the recruiter will be shown a "randomize" button, and will receive the assignment ("Wear LifeVest" or "Do Not Wear LifeVest") upon activating the button since participants and clinical site clinicians are not blinded to treatment assignment. After randomization, the group assignment may be printed by the clinical sites from the website along with group-specific study instructions for physicians and participants.

If there is any question regarding eligibility for randomization, the clinical site personnel will contact the CCC for adjudication prior to seeking randomization. Every effort will be made to minimize protocol deviations regarding participant eligibility for the study, including quality control procedures to assure that the ejection fraction (EF) entry criterion is accurate.

1.5.7 Participant Retention

We will make every effort to ensure that participants are not lost to follow-up nor drop out of the study. At the initial screening and enrollment visit, the clinical site will record identifying information including address, phone number, social security number and the name, address and phone number of one family member and two close friends able to locate the participant.

We do not expect many participants to be lost to follow-up given the short 3 month time frame. All the participants will be recovering from a recent MI; therefore, they are less likely to travel far or be non-compliant. Two thirds of the participants will also be wearing a LifeVest during these 3 months. The LifeVest will be a reminder to participants that they are in the study and need to maintain close follow-up with the study coordinators. In addition, participants wearing the LifeVest will be required to send data via a modem (integrated into the LifeVest monitor) on a weekly basis. This will allow clinical sites to track participants on a weekly basis. The Data Management System will identify participants who have missed transmissions and post reports on the study website accessed by site coordinators. These will be followed up by e-mail alerts.

1.5.8 Predictor Variables

The primary predictor variable will simply be randomization to LifeVest or no LifeVest.

1.5.9 Outcome Variables

The outcome measures are outlined in Table 3. The primary outcome is sudden death and death due to ventricular arrhythmia at 3 months (90 days) after randomization. We will use the following definition of Sudden Death:

> For witnessed deaths, sudden cardiac death will be defined as an unexpected, non-traumatic, non-self-inflicted fatality in otherwise stable participants who die within one hour of the onset of the terminal symptoms. For persons dying more than one hour after a cardiac arrest from a ventricular arrhythmia, the Non-Sudden Death due to Ventricular Arrhythmia category should be used.
>
> For unwitnessed deaths, participants will meet the definition of sudden death if they are found dead within 24 hours of being well, assuming there is no evidence of another cause of death during that time period. Device arrhythmia and autopsy results may be used when available. For unwitnessed deaths when the participant was found dead more than 24 hours after last being seen, no device arrhythmia data are available, no autopsy results are available and no other information is available regarding the cause of death, the Indeterminate category should be used.

We also include non-sudden deaths due to ventricular arrhythmia in the primary outcome definition. Deaths are categorized as such when a person suffers a cardiac arrest from an acute ventricular arrhythmia, is resuscitated and admitted to the intensive care unit, and then dies several days after the arrest from complications (e.g., neurological damage). Secondary outcomes for VEST are total mortality, non-sudden death and other cause-specific mortality (non-sudden fatal MI, other cardiac death, non-cardiac death, and indeterminate cause of death), hospitalization for MI, congestive heart failure, stroke/transient ischemic attack, ventricular arrhythmias, adverse events, LifeVest compliance, eventual ICD implantation, quality of life, and resource utilization/cost. The wearable defibrillator can do continuous ECG recording and monitor time worn. Therefore, data for several of the secondary outcomes that are analyzed within the intervention group will come from the LifeVest transmissions.

Outcome Adjudication: The DCC will direct the adjudication of study outcomes. Assigning cause-specific mortality, as is required for the primary VEST outcome and a number of important secondary endpoints for VEST, can be difficult. Cardiac electrophysiologists actively engaged in clinically relevant patient care will be employed to provide expert opinions regarding these endpoints. The Endpoints Director will manage the adjudication process designed to categorize arrhythmias and deaths appropriately, minimize bias by blinding adjudicators to treatment assignment, and protect against unnecessary disclosure of protected health information. Table 3 lists the primary and secondary outcomes, the data source, and whether or not each endpoint requires adjudication. Definitions for each endpoint are provided below.

Cause-specific Mortality and Non-Fatal Cardiovascular Events: Deaths will be reported by family members or clinicians, or detected by clinical sites when study participants fail to show up for scheduled examinations or miss scheduled data transmissions. Social security death index searches will be performed for all participants lost to follow-up for whom vital status is unknown in the U.S.. Hospitalizations will be reported by participants at or between scheduled examinations or phone calls. Sites will notify the DCC within 48 hours of learning about a death or cardiovascular hospitalization, and will then have eight weeks to obtain a death certificate; all discharge summaries for any hospitalizations occurring within 1 month of the index death/hospitalization, and narratives from personal contacts of deceased participants (listed at recruitment) regarding manner and circumstances of death. All personal identifiers and mention of treatment assignment (for the VEST arm) will be carefully stripped by clinical site staff to the extent possible. For all deaths, the DCC will redact any mention of the LifeVest in participants assigned to VEST, and add fake redaction in participants assigned to NO VEST so that adjudication of cause of death will be blinded. ECG data from the LifeVest will NOT be used to adjudicate fatal outcomes for VEST,

because this information will not be available on participants without a LifeVest, and use might induce bias from differential measurement error. Complete packets will be assembled by the DCC and read independently by two adjudicators. Every death will be categorized according to the cause-specific mortality and non-fatal cardiovascular event categories described in Table 3. Disagreements will be resolved by consensus, involving a third adjudicator when required.

Ventricular Arrhythmias: Electronic rhythm strips recorded by the LifeVest will be uploaded to the study database via electronic data transfer from ZOLL. Strips will be presented to adjudicators in batches, with study ID numbers and adjudication forms and read independently by two cardiac electrophysiologists. Adjudicators will determine whether the LifeVest therapy was "appropriate" or "inappropriate" based primarily on the presence or absence of a true ventricular arrhythmia. Discordances will be resolved by consensus, involving a third adjudicator when required.

Quality of Life: Quality of life outcomes will be measured using self-administered questionnaires mailed to participants 1-2 weeks prior to the 3 month visit. QOL will be assessed using the SF-36 for health related quality of life, the CES-D to measure depression, the Spielberger STAI to measure anxiety, and the MOS sleep scale to measure sleep patterns. The EQ-5D will be administered to measure subjective health status, and the International Physical Activity Questionnaire (IPAQ) short format for physical activity. The Florida Patient Acceptance Scale (FPAS) will be included to measure device acceptance in those randomized to the LifeVest.

Economic Outcomes: Cardiovascular hospitalizations, visits to emergency rooms, unscheduled cardiovascular outpatient visits and adverse events will be collected at the follow-up visits by self-report, including the reasons for admission and length of stay. All admissions will be assigned to a DRG based on participant report and review of medical records obtained to document clinical outcomes. The number of physician visits, major tests, and medications will be collected using a brief survey. For VEST, we will compare costs over follow-up between participants assigned to the LifeVest and those assigned to usual care. We will analyze whether the costs of management, apart from the cost of the LifeVest itself, are lower in the vest assigned participants. This approach will allow us to determine if there are any cost savings in the VEST arm participants that will offset the expected, planned costs of the intervention. In a secondary analysis, we will compare total cost (i.e., costs including the cost of the LifeVest) between the two randomized groups, and calculate confidence limits on the cost difference between the two groups using a bootstrap resampling approach.

1.5.10 Adverse/Outcome Events

Most symptoms, signs and clinical events will be captured by questionnaire during routine scheduled clinic and telephone visits. Data collection forms are specifically designed to capture known adverse events from the LifeVest including physical discomfort (rash, etc.). Inappropriate shock events will be adjudicated, as above. Site investigators will make a determination for all deaths and hospitalizations about whether the event was related to participation in the study; all such events will be adjudicated and summarized for the Data Safety Monitoring Board (DSMB).

1.5.11 Analysis Plan for VEST

Treatment effects on the primary outcome, sudden death and death due to ventricular arrhythmia, will be assessed using stratified exact methods to compare cumulative incidence in the VEST and control groups at 60/90 days. An exact test of the primary null hypothesis of no treatment effect will be conducted using a two-sided alpha of 5%. This analysis will be by intention to treat (ITT), without regard to adherence to the assigned study intervention or other aspects of care. The analysis will be jointly

Table 3. Outcome measures for VEST.

OUTCOMES	PRIMARY/SECONDARY	DATA SOURCE	ADJUDICATED
Sudden death mortality	**Primary**	Records/interviews†	Yes
All-cause (total) mortality	Secondary	Records/interviews†	Yes

Cause-specific mortality			
Non-sudden death	Secondary	Records/interviews†	Yes
Ventricular Arrhythmia Death	**Primary**	Records/interviews†	Yes
Other Fatal Arrhythmia	Secondary	Records/interviews†	
Non-Sudden Fatal MI	Secondary	Records/interviews†	Yes
Fatal Congestive Heart Failure	Secondary	Records/interviews†	Yes
Other Cardiac Death	Secondary	Records/interviews†	Yes
Fatal Stroke	Secondary	Records/interviews†	Yes
Other Non-cardiac Death	Secondary	Records/interviews†	Yes
Indeterminate Cause of Death	Secondary	Records/interviews†	Yes
Time to death after 1st VT/VF episode	Secondary	Records/ICD/Reveal	Yes
Non-Fatal Cardiovascular Events			
MI	Secondary	Records/interviews†	Yes
Atrial fibrillation	Secondary	Records/interviews†/ ICD/Reveal	Yes
Congestive heart failure	Secondary	Records/interviews†	Yes
Stroke	Secondary	Records/interviews†	Yes
LifeVest Events			
Ventricular Tachyarrhythmia	Secondary	LifeVest	Yes
LifeVest Shocks delivered	Secondary	LifeVest	Yes
30 Beats of VT (CL 330-370 msec)	Secondary	LifeVest	Yes
Inappropriate Shock - SVT	Secondary	LifeVest	Yes
Inappropriate Shock - Malfunction	Secondary	LifeVest	Yes
Time to 1st episode of VT/VF	Secondary	LifeVest	Yes
Adverse Events			
Device-attributable Death or Hospitalization	Secondary	Records/interviews†	Yes
Device-related Symptom or Sign	Secondary	Data Form	No
Device Change-out	NA	Data Form	No
Other Adverse Event	Secondary	Data Form	No
Vest Compliance	Secondary	LifeVest	
ICD Implantation	Secondary	Data Form	No
Quality of Life	Secondary	QOL Instruments	No
Resource Utilization/Cost	Secondary	Data form	No

† - Includes information from medical records, death certificates, interviews of next-of-kin or personal physicians, and National Death Index searches
VF – Ventricular fibrillation; VT – Ventricular tachycardia; SVT – Supraventricular tachycardia; ICD – Implantable cardioverter defibrillator

stratified by length of follow-up period (to account for the higher expected rate in patients with 90 day follow-up), and randomization stratum, as jointly defined by EF and receipt of PCI and/or CABG during the hospitalization for the index MI.

We will also conduct a secondary "modified intention-to-treat" analysis of sudden death and death due to ventricular arrhythmia, total mortality, and other secondary outcomes. For this analysis, follow-up time will start at the time of discharge instead of randomization, and end 60/90 days after discharge, and participants who are randomized but die before discharge from the index hospitalization will be excluded. For death outcomes, this analysis will use the stratified exact methods specified for the primary analysis; for more common secondary outcomes, asymptotic methods will be considered.

We will also analyze treatment effects on overall mortality and non-sudden death, non-fatal cardiovascular events, ventricular arrhythmias, adverse events, LifeVest compliance, ICD implantation, quality of life and resource utilization/cost. For rare outcomes, exact methods will be used, as for the primary endpoint. For VEST therapies and hospitalizations, we will use the Anderson-Gill extension of the Cox model for repeated events, with robust standard errors, to better capture information from high-risk participants with repeated VEST therapies or hospitalizations.

We will also conduct a secondary, "as treated" analysis of sudden death and death due to ventricular arrhythmia, total mortality, and other secondary outcomes. The primary ITT analysis will estimate effectiveness of the vest, averaged over variations in compliance. We will attempt to estimate the efficacy of the vest for prevention of sudden death and death due to ventricular arrhythmia as well as total mortality using survival models treating observed vest use as a time-dependent covariate. For sudden death and death due to ventricular arrhythmia, we will

use a Fine-Gray model treating other deaths as competing risks; a standard Cox model will be used for total mortality.

1.5.12 Sample Size Calculations

When the trial was originally designed, the sample size for the VEST study was estimated to be 1,890. This assumed a power of 80%, with a 2-sided alpha of 0.05 and a 2:1 randomization scheme. The VEST sample size was carefully computed using data-based estimates of the following factors:

1. Mortality due to sudden death in the first 2 months following an MI in patients with EF≤35% is 2.4%. The VALIANT Study, the EPHESUS Study, and the DINAMIT Study are three recent studies reporting on mortality and sudden death rates in the early period following an MI in populations similar to our study population. *A meta-analysis of these three studies populations gives a summary estimate for sudden death rate of 2.4%.*

2. Mortality due to sudden death in the first 3 months following an MI in patients with EF≤35% is 3.0%. Using month-by-month data on sudden death in VALIANT, we estimate that extending follow-up from 2 to 3 months will increase the sudden death rate by 25%, from 2.4% to 3.0%. This accounts for declines in the sudden death rate in the weeks following MI.

3. Mortality due to ventricular arrhythmias in the first 3 months following an MI in patients with EF≤35% is 2.73%. The wearable defibrillator vest will be effective at reducing only sudden death due to a ventricular arrhythmia. The preliminary data from the wearable defibrillation vest shows that 91% of all sudden cardiac arrests are due to ventricular arrhythmias. This is consistent with estimates in the literature. *Therefore, 91% of 3.0% would give us an expected mortality of 2.73% due to ventricular arrhythmia.*

4. The effectiveness of the wearable defibrillator to reduce sudden death due to ventricular arrhythmias will be 71.9%. Previous analyses show that the LifeVest conversion success rate is 98% for syncopal VT/VF. Based on early experience in VEST and planned changes in randomization procedures, we have targeted an intention-to-treat compliance rate with the LifeVest of 70%. This means that participants assigned to the LifeVest will wear it for 70% of all hours in the 3 months following randomization, including days when the LifeVest is not worn at all. However, since compliance and event rates are both anticipated to be highest in the earliest weeks of the trial we anticipate the LifeVest will be used during more than 70% of sudden death events. Thus, we estimate that the LifeVest will reduce sudden death due to syncopal VT/VF by 71.9%.

5. Given the above assumptions, we estimate an overall sudden death rate of 3.0% in the control group and 1.02% in the wearable defibrillator group (67% reduction in sudden death). The absolute reduction in mortality is the mortality from ventricular arrhythmia (2.73%) times the effectiveness of the LifeVest (71.9%) = 1.98%. *Thus, the sudden death rate in the defibrillator LifeVest group is expected to be the mortality in the control group minus the absolute reduction or 3.00%-1.98% = 1.02%.*

6. Given the short follow-up period (3 months) and strong efforts to collect complete data, we anticipate minimal loss to follow-up and minimal crossover. Crossover in the treatment group (LifeVest group) is accounted for in #4 above (some patients will not tolerate the LifeVest). Given that the LifeVest is only available by prescription, we expect that crossover from the control group to the treatment group will be exceedingly rare.

7. A power of 80%, with a 2-sided alpha of 0.05 and a 2:1 randomization scheme. Using these estimated event rates, a 2:1 randomization scheme and the standard formula for two-group comparisons of proportions, *we will need a sample of 1260 in the wearable defibrillator group and 630 in the control group, or 1890 total participants.*

Updating the Sample Size for VEST: We recognized that this sample size calculation is sensitive to the values of the inputs noted above. This raises the concern that the VEST trial might fail to reach firm conclusions despite the

anticipated efficacy. Rates of total mortality, sudden death and death due to ventricular arrhythmia, and LifeVest compliance are especially important drivers of sample size, and these are easily monitored during follow-up. We therefore plan to update our sample size after 1000 participants have completed their VEST follow-up and then again after 1500 participants have completed follow-up. We will use interim overall rates of total mortality and sudden death and death due to ventricular arrhythmia, as well as LifeVest compliance and crossover rates (off-protocol use of the LifeVest in the NO VEST arm), in conjunction with our original assumptions about the proportion of all sudden deaths that are due to ventricular arrhythmias and the efficacy of the LifeVest in preventing these potential events. We will also account for time in the hospital after randomization but before discharge (using real estimates of time-to-discharge from the study), during which the LifeVest is typically not worn and when we expect no differential effect on mortality to be induced by assignment to VEST. Because this procedure is blinded to treatment assignment, no meaningful inflation of the type-I error rate is expected.[11,12]

The following limits will be adhered to when updating the sample size:

- The sample size will be updated only if the revised sample size is more than 10% larger than the planned value of 1900, i.e., greater than 2100.
- The updated sample size will not exceed 4,000 (twice the current planned sample size).
- No decrease in the planned sample size will be allowed (outside of the direction of the DSMB).

FINAL SAMPLE SIZE: In October 2015, after 1500 participants completed follow-up, the VEST Data and Safety Monitoring Board (DSMB) reviewed the blinded sample size re-estimation calculations and was concerned that with the estimated power at the current sample size (n=1890) there is a substantial likelihood of type II error. Therefore, the DSMB recommended that the VEST sample size be increased in order to achieve an estimated power of at least 70%, with a composite sudden death rate in the trial of 1.66%.

On April 25, 2016, the VEST Steering Committee approved the increase in sample size to a total of 2300 participants.

1.6 DATA REPOSITORY

All primary data (including that collected via questionnaire, testing, LifeVest interrogation) will be stored in a study-wide database.

1.7 VEST REGISTRY

In order to determine long-term outcomes in patients who are eligible and enroll to participate in VEST, all patients in the VEST Registry will have at least yearly follow-up to determine vital status, most recent EF, whether an ICD has been implanted and whether they have had any cardiovascular hospitalizations/events. These will be obtained by searching medical records and death indexes, and by interviewing participants by phone.

1.7.1 U.S. National Death Index Search at End of the Trial

At the end of the trial, we will perform a National Death Index search for U.S. participants with unknown vital status to obtain data on the primary (sudden death) and secondary (all cause mortality) study outcomes. Confirmation of VEST participant deaths is of vital importance, in order to reduce the risk of missing data bias which may impact the robustness of the final trial results. The International Conference on Harmonization (ICH) guidelines on Statistical Principles for Clinical Trials[14], which has been adopted by the U.S. FDA, state “Missing values represent a potential source of bias in a clinical trial. Hence, every effort should be undertaken to fulfill all the requirements of the protocol concerning the collection and management of data.”

The proposed NDI search qualifies for a waiver of consent. Federal regulation 45 CFR 46.116(d) establishes four criteria for waiving consent or altering the elements of consent in minimal risk studies.

1. The research involves no more than minimal risk;

- *The NDI search involves no more than minimal risk,* since the only potential risk of the NDI search is a possible loss of confidentiality for VEST participants that have unknown vital status at the end of the study period. Based on the current rate of unknown vital status in VEST to date (as of June 2016), it is estimated that only 6% of all randomized participants (6% of 2300 = 138 participants) will have unknown vital status at the end of the trial. The UCSF Data Coordinating Center will do the following to minimize the risk of a loss of confidentiality: (1) access to NDI search data that includes possible identifiers will be limited to the unblinded statistician and the unblinded DSMB project director; (2) NDI search data with identifiers will be temporarily stored on a restricted access server that is encrypted and password protected. This is necessary for the data to be reviewed for accuracy during the matching process; (3) After completion of the matching process and vital status for the approx. n=138 participants has been determined, all electronic (and hardcopy data, if any) NDI data containing identifiers will be destroyed.

2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
   - *The NDI search will not adversely affect the rights and welfare of the VEST participants,* since the only potential risk of the NDI search is a possible loss of confidentiality for VEST participants that have unknown vital status (approx.. n=138).

3. The research could not practicably be carried out without the waiver or alteration; and
   - *There is no other option for obtaining the data necessary to answer this trial's key research objective regarding the primary study outcome (death) without the NDI search for the participants with unknown vital status at the end of the study period*. Prior to classifying a participant as having "unknown vital status", the clinical sites will attempt to obtain vital status using all available options, as possible (e.g., contacting the participant using all available contact information (i.e., U.S. mail, email, phone), contacting family/friends, search of available medical records, search of public records, including obituaries and genealogy websites). Only after these options have been exhausted will the participant be included in the list of individuals to be submitted to the NDI. It would not be possible to obtain consent to do the NDI search for these participants with "unknown vital status" at the end of the trial.

4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
   - *The NDI search will only provide results for the potential confirmation of death outcomes in VEST participants. Therefore, this criteria does not apply.*

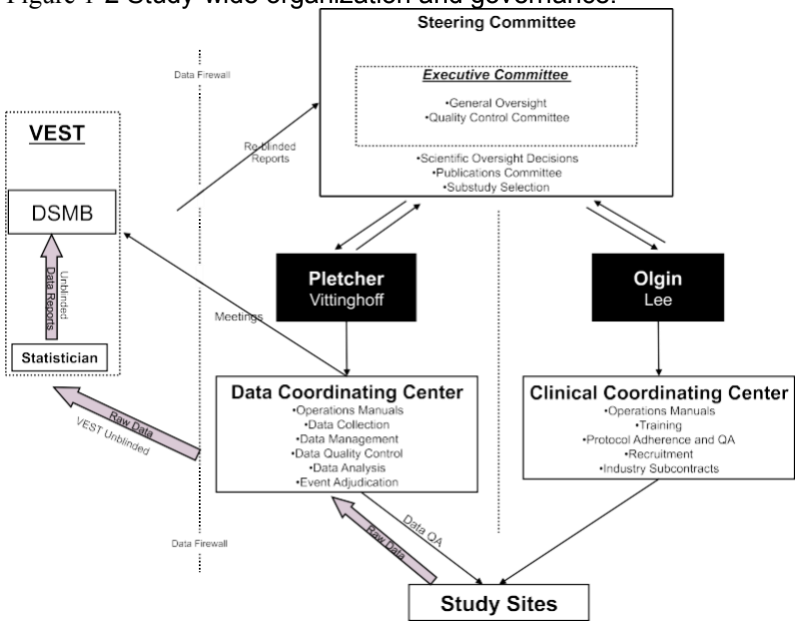
PART 2. COORDINATING CENTERS' PLAN

2.1 ORGANIZATION AND ADMINISTRATION

The study-wide organization chart is shown in Figure 1-2.

2.1.1 Coordinating Centers

Figure 1-2 Study-wide organization and governance.



There are two separate and independent coordinating centers for VEST. A **Clinical Coordinating Center (CCC),** led by Jeffrey Olgin, MD, responsible for day-to-day operations of the study as it relates to participant enrollment and clinical site administration, and a **Data Coordinating Center (DCC),** led by Mark Pletcher, MD, MPH responsible for assuring excellence of all aspects of data acquisition and analysis for the study. The PIs and staff of the coordinating centers will work cooperatively to assure the successful achievement of the studies' specific aims. One of the reasons for separate coordinating centers is to assure that the PI and staff members of the CCC do not have access to the study database, which resides with the DCC, and remain blinded to study outcomes until all participants have completed the clinical trial.

The CCC manages the clinical sites, which includes overseeing the quality of clinical measurements obtained in the study and ensures adherence to the study protocol. The CCC is responsible for all aspects of participant recruitment. This includes development of the operations manual, training activities, getting sites up and running, facilitating recruitment strategies and monitoring recruitment progress. The CCC will adjudicate decisions regarding participant eligibility. The CCC is also responsible for managing and oversight of clinical site monitoring. Finally, the CCC is responsible for preparing the agenda and materials for Steering Committee meetings.

The primary functions of the DCC include creation of tamper-proof systems for randomization and analysis of blinded data analysis, development of the data forms, training and certification of clinical site staff in the data management system, randomization of participants for the intervention phase of the study, acquisition of data from the clinical sites and monitoring devices, data quality control, event adjudication, and data analysis. The DCC is also responsible for coordinating and supporting the activities of the DSMB.

2.1.2 Committees and Governance

Steering Committee. The Steering Committee will be responsible for general scientific oversight and progress of the study. The Steering Committee will be responsible for overseeing study progress including ancillary studies, and for scientific policies, integrity and direction. It will appoint the analysis and publications committee and writing groups, ensuring that information from the study is disseminated in the scientific literature and at scientific meetings. The committee will be chaired by Dr. Olgin and will be comprised of the CC co-investigators (Drs. Pletcher and Lee), statistician (Dr. Vittinghoff), representatives from ZOLL, select consultants and site PIs. Industry representatives will be non-voting members on the committee. A list of Steering Committee Members is attached. The Steering Committee will meet at least twice in the 1st year and then at least once yearly in person, videoconference or teleconference.

Executive Committee. An executive subgroup of the Steering Committee will be responsible for decisions that require attention between Steering Committee meetings, and for major financial, administrative, and operational

decisions. The Executive Committee will consist of Dr. Olgin (chair), Dr. Lee, Dr. Pletcher, Dr. Vittinghoff, and one representative from ZOLL. Industry representatives will be non-voting members on the committee.

Quality Control (QC) Committee. The QC Committee will be responsible for assuring that the methods and procedures of the study are carried out uniformly and with a high level of quality. It will be co-chaired by Dr. Pletcher (DCC) and Dr. Lee (CCC), with Dr. Pletcher leading the portion of the meeting devoted to data quality, and Dr. Lee leading the portion devoted to clinical procedures. Members of the committee will include the project directors of the DCC and CCC, representatives from all clinical sites (study coordinators), and ad hoc participation by representatives from ZOLL and study-wide consultants when needed.

Data Safety Monitoring Board (DSMB). An independent DSMB will be responsible for reviewing the outcome data obtained at regular intervals to recommend decisions designed to assure the safety of the participants, the integrity of the scientific effort, and the optimal timing for ending VEST recruitment.

2.2 OPERATIONS MANUAL, FORMS

In consultation with the Steering Committee and Investigators in the CCC, the DCC will design and produce the data collection forms for the study during the planning phase. The DCC and CCC will jointly develop a comprehensive Operations Manual, updating it as needed with careful version control. The Operations Manual will serve as a guide for training clinical site personnel, as well as for standardizing procedures for data acquisition and editing during the study.

2.3 DATA MANAGEMENT SYSTEM

The DCC has a customized hybrid of off-the-shelf software combining decentralized data submission, centralized and remote data editing, and a centralized database structure designed to collect, transfer and store data. In this system, data are collected on Teleform forms and transmitted electronically (via fax) to the DCC by remote clinical sites. Electronic data are received at the DCC and assessed by both automated and manual processes before being entered into the study-wide database. Every 24 hours, data discrepancies (queries) are automatically generated identifying potential errors in the data. Clinical site staff members access their own data queries via the secure web site and resolve them in a timely manner. An audit trail of changes to the data is automatically produced. Data from outside sources, such as central reading centers or core laboratories, is integrated into the study-wide database.

Study-wide Communications/Website: Most communication and problem-solving regarding data management issues will occur through a central website provided by our data management system. The private, secure website provides access to a study-wide directory with phone numbers, fax numbers and e-mail addresses of all clinical sites and core labs. It serves as a central repository for study documents including the operations manual, meeting and conference call minutes, all-site emails, and all required data forms, which can be directly downloaded from the website.

Data Collection and Editing at the Clinical sites: Our data system uses machine readable forms and Internet technology to provide rapid and timely access to accurate and high quality data. The clinical sites complete the machine-readable data forms and transmit them to the DCC using standard fax machines. All that is required at the participating sites is a fax machine and a high-speed Internet connection. When the data arrives at the DCC, the data forms are received as an electronic image and are automatically evaluated using Teleform software. As each form is verified by a DCC staff member, the data is automatically written to the study's Microsoft SQL Server database.

Each hour, all of the study data is subjected to error-checking programs that check for completeness, consistency and validity. The results of the error-checking procedures are posted to the study web site where clinical site personnel check it daily to both confirm that the DCC has successfully received all of the faxed forms and to address the errors that have been detected. In all such procedures, site personnel will have access only to their own site's data.

Data Transmission from Reading Centers, Laboratories: For data that is electronic in nature, such as from the LifeVest, the DCC will establish a system for efficient transfer of this data directly to the DCC database andwill monitor it for completeness and quality.

2.4 COMPUTER AND DATA SECURITY

The DCC follows standard operating procedures (SOPs) for computer system security to ensure the confidentiality and validity of study data. The SOPs are designed to prevent unauthorized access and limit authorized access to our computer systems and are in compliance with established standards for Information Technology Security. Our network is privately maintained, hardware fire-walled and none of the workstations or database servers can be directly addressed from outside the Local Area Network. Study website and database access requires a network domain account with appropriate account-specific permission on the database. All requests for new accounts and access to the database must be documented by a System Access Request Form signed by the project director.

All study data will be stored on SQL servers at the DCC at 185 Berry St., San Francisco. Each server is backed-up nightly to disk and mirrored to a "failover" site at our co-location facility at 650 Townsend St., San Francisco. These two sites have copies of the study database and all associated systems required to carry on the study in the event of a disaster in one of the locations. In addition, backup copies of the entire enterprise (databases, user workstations, file servers, etc) are archived in Sacramento, California by Recall, Inc. This will protect the study data in case of a natural disaster affecting the San Francisco Bay Area. All servers are housed in a new (2005) state-of the-art secure server room. Access to the server room is via a limited access suite occupied by our Information Technology (IT) staff. Both the suite and server room doors are fitted with an Access Control System. Only critical IT staff members are allowed to enter the room. All others who enter the server room (e.g., air conditioning repairman) must be accompanied by a member of the IT staff and their visit is logged.

Website communications are encrypted at the 128-bit level using an SSL certificate issued by Verisign (Verisign, Inc, Mountain View, CA). All servers are protected from viruses by Network Associates Netshield 4.x, Groupshield, and VirusScan Enterprise 7.x (McAfee, Santa Clara, CA). This software automatically checks for virus signature file updates from Network Associates' FTP and HTTP sites once an hour. All anti-virus software is monitored and IT personnel are notified in the event that the software stops functioning on a particular server.

2.5 TRAINING, SITE VISITS AND QUALITY CONTROL

Central Training Session: A central training session for clinical site personnel will be held prior to the start of participant enrollment in the study. All staff will be trained on use of the LifeVest, study protocols, and the data system. At the initial training session, the clinical site coordinators will receive the Operations Manual, which will serve as a guide to the training session. The subsequent expectation is that if a trained staff member leaves during the study, he or she would train his/her replacement. Since that is not always possible, we have found that new staff members are fairly readily able to learn the procedures of the study and the data system by reading the Operations Manual, either a site visit to a nearby site or from the CCC, and frequent telephone and email contact with the CCC and DCC.

Site Visits to Clinical Sites: Every clinic will be site visited soon after starting recruitment by a representative of the CCC, DCC or industry partner, and a structured review of facilities and equipment, procedures, files, systems and data will be carried out. In addition there may be early visits by representatives of ZOLL to help maximize LifeVest adherence as discussed above. Subsequent site visits will be scheduled as needed, and to address quality control issues that come to light in the clinical and data monitoring procedures described below. In addition, routine site monitoring by CCC, DCC or ZOLL will occur throughout the study duration and at close-out.

Data Quality Control and Verification at the DCC: The distributed nature of the data system emphasizes error identification and resolution at the clinical site soon after entry via the data query system described above. The primary advantage of this system is to concentrate data editing closer to the data collection process, which will result in the following benefits: (1) site personnel will have better

recollection of the data making resolution easier and more efficient, (2) data errors will not build up over time and remain manageable, (3) early recognition of errors by site personnel can prevent them from making the same errors again, and (4) data will be cleaner for interim reports and presentations to the DSMB. Once the data arrive at the DCC, there is a multi-step approach for data verification and quality control, including:

- 100% visual verification of all data values as interpreted by Teleform Reader optical character recognition (OCR) against scanned images of the completed source data collection forms
- Data form specific insertion criteria (via SQL triggers) to prevent duplicate or incorrectly identified form entry
- Missing forms reports based on temporal or logical relationships, generated by a batch Visual Basic application. These reports will be made available on the study web site.
- Comprehensive univariate and multivariate field discrepancy identification by a Visual Basic query generation application. These queries will involve within-form and cross-form comparisons and will appear on the study web site for real-time resolution by the clinical sites.
- Complex and resource-intensive second-tier data cleaning in SAS.

The data management system provides an audit trail that tracks what variables have been changed, the date they were changed, and which staff member made the changes. In addition, site PIs or Co-PIs will be required to review and approve each participant dataset to ensure data integrity.

Data Monitoring: The DCC will design reports that will be accessible to all sites from the study website. Most reports will display data stratified by clinical site, introducing a healthy competition between centers. Examples of such monitoring reports include: recruitment reports comparing goal versus actual recruitment rates by center; visit compliance reports comparing the number of expected visits to actual visits for each protocol-required visit; participant retention reports indicating the number of participants active, completed, lost, etc; missing forms reports; missing data reports (for specific critical data fields or variables), etc. These reports will be reviewed every month on Quality Control Committee conference calls and periodically brought to the attention of the Steering Committee. These types of monitoring reports will also be presented to the DSMB along with outcomes data. Such reports are critical to identify study-wide problems as well as problems specific to particular clinical sites, and since the reports are available "real-time", problems can be addressed before they become entrenched.

2.6 STATISTICAL ANALYSIS AND DISSEMINATION

The DCC will be primarily responsible for statistical analysis of the research questions posed by VEST. The data will reside with the DCC and will be analyzed by DCC personnel for interim DSMB reports and for publications, presentations and other dissemination activities according to the plan described in section 1.5.11 and with scientific oversight by the Steering Committee.

2.7 CLOSE OUT

During the final 6 months of the study, data quality control checks will be completed and a final version of the database files created. In cooperation with the Steering Committee, DCC and CCC staff will participate in preparation of the main report and other analyses and writing tasks. The DCC and CCC will coordinate the analysis, presentation and publication of study findings upon study completion. The Steering Committee will act as a Publications Subcommittee charged with developing a list of publication topics together with authorship lists.

A set of study documents (protocol, forms, questionnaires and operations manual) will be archived. Database files, as well as statistical analysis files, will be documented and archived.

References

1. Task Force Members, Thygesen K, Alpert J, White H, Group B, Jaffe A, Apple F, Galvani M, Katus H, Newby L, Ravkilde J, Group E, Chaitman B, Clemmensen P, Dellborg M, Hod H, Porela P, Group I, Underwood R, Bax J, Beller G, Bonow R, Van Der Wall E, Group I, Bassand J, Wijns W, Ferguson T, Steg P, Uretsky B, Williams D, Group CI, Armstrong P, Antman E, Fox K, Hamm C, Ohman E, Simoons M, Group GP, Poole-Wilson P, Gurfinkel E, Lopez-Sendon J, Pais P, Mendis S, Zhu J, Group I, Wallentin L, Fernández-Avilés F, Fox K, Parkhomenko A, Priori S, Tendera M, Voipio-Pulkki L, Guidelines ECfP, Vahanian A, Camm A, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen S, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano J, Reviewers D, Morais J, Brener S, Harrington R, Morrow D, Sechtem U, Lim M, Martinez-Rios M, Steinhubl S, Levine G, Gibler W, Goff D, Tubaro M, Dudek D, Al-Attar N. Universal definition of myocardial infarction: Kristian Thygesen, Joseph S. Alpert and Harvey D. White on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. *Eur Heart J.* 2007;28(20):2525-2538.

2. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation.* 2001;104(18):2158-2163.

3. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med.* 2004;351(24):2481-2488.

4. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med.* 2002;346(12):877-883.

5. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med.* 2005;352(3):225-237.

6. Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death--executive summary: A report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death) Developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Eur Heart J.* 2006;27(17):2099-2140.

7. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, Hochman JS, Krumholz HM, Kushner FG, Lamas GA, Mullany CJ, Ornato JP, Pearle DL, Sloan MA, Smith SC, Jr., Alpert JS, Anderson JL, Faxon DP, Fuster V, Gibbons RJ, Gregoratos G, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Ornato JP. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction; A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of patients with acute myocardial infarction). *J Am Coll Cardiol.* 2004;44(3):E1-E211.

8. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, 3rd, Steward DE,

Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC, Jr. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction--2002: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). *Circulation.* 2002;106(14):1893-1900.

9. Fuster V, Rydén L, Cannom D, Crijns H, Curtis A, Ellenbogen K, Halperin J, Le Heuzey J, Kay G, Lowe J, Olsson S, Prystowsky E, Tamargo J, Wann S, Smith S, Jacobs A, Adams C, Anderson J, Antman E, Halperin J, Hunt S, Nishimura R, Ornato J, Page R, Riegel B, Priori S, Blanc J, Budaj A, Camm A, Dean V, Deckers J, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano J, Guidelines ACoCAHATFoP, Guidelines ESoCCfP, Association EHR, Society HR. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation.* 2006;114(7):e257-354.

10. Wilkoff B, Stern R, Williamson B, Wathen M, Holloman K, Fieberg A, Brown M. Design of the Primary Prevention Parameters Evaluation (PREPARE) trial of implantable cardioverter defibrillators to reduce patient morbidity [NCT00279279]. *Trials.* 2006;7:18.

11. Gould AL. Sample size re-estimation: recent developments and practical considerations. *Statistics in medicine.* 2001;20:2625-2643.

12. Gould AL. Interim analyses for monitoring clinical trials that do not materially affect the type I error rate. *Statistics in medicine.* 1992;11(1):55-66.

13. Ikeda T, Saito H, Tanno K, Shimizu H, Watanabe J, Ohnishi Y, Kasamaki Y, Ozawa Y. T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. *Am J Cardiol.* 2002;89(1):79-82.

14. International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials [E9]. 5 February 1998.

Appendix 1.A Abbreviations

ACC	American College of Cardiology
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
CABG	Coronary Artery Bypass Grafting surgery
CCC	Clinical Coordinating Center
CCU	Coronary Care Unit
CHF	Congestive Heart Failure
CMS	Centers for Medicare Services
CRF	Case Report/Record Form
CRT	Cardiac Resynchronization Therapy
DCC	Data Coordinating Center
DI	Detection Interval
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EF	Ejection Fraction
FVT	Fast VT
HRV	Heart Rate Variability
ICD	Implantable Cardioverter Defibrillator
IRB	Institutional Review Board
ITT	Intent-to-Treat
MI	Myocardial Infarction
MVP	Minimal Ventricular Pacing
NIH	National Institutes of Health
NHLBI	National Heart, Lung and Blood Institute
NID	Number of Intervals to Detect
NIPS	Non-invasive Programmed Stimulation
NSVT	Non Sustained Ventricular Tachycardia
QOL	Quality of Life
RNID	Number of Intervals to Redetect
PCI	Percutaneous Coronary Intervention
SVT	Supraventricular Tachycardia
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

VEST
Statistical Analysis Plan

Version 1.0 to Version 1.1 (5/12/2012)

1. Primary endpoint revised from sudden cardiac death to sudden cardiac death or non-sudden death to ventricular arrhythmia (Section A, page 1).

Version 1.1 to Version 1.2 (12/5/2016)

1. Analysis of primary endpoint revised to use a simple chi-square test rather than exact stratified methods (Section A, page 1).
2. Section on Exploratory Analysis of Compliance added (Section B.4, page 2).

Version 1.2 to Version 1.3 (3/2/2017)

1. Plan is added for weighted sensitivity analysis of primary outcome omitting patients with indeterminate cause of death or unknown vital status (Section B.1.3)

VEST
Statistical Analysis Plan

A. Primary Analysis

Treatment effects on the primary outcome, sudden death or non-sudden death due to ventricular arrhythmia, will be assessed using a chi-square test to compare incidence proportions in the VEST and control groups at 60/90 days after randomization. The test of the primary null hypothesis of no treatment effect will be conducted using a two-sided alpha of 5%. This analysis will be by intention to treat (ITT), according to treatment assignment, without regard to adherence to the assigned study intervention or other aspects of care.

B. Secondary Analyses

B.1. Sensitivity Analyses

Results will be checked for robustness in three planned sensitivity analyses.

1. *Modified intention to treat.* We will omit from this analysis, patients who do not survive until discharge from the index hospitalization, and the 60/90 day follow-up will begin at the later event of randomization or discharge. The rationale is that the vest is essentially never worn in hospital, and so can provide no protection until after discharge. Although mortality is highest soon after a serious MI, close in-hospital monitoring is expected to keep the in- hospital death rate low. As part of this analysis, we will characterize times from randomization to discharge using histograms, stratified by group.

2. *Adjustment for baseline imbalances.* If we find substantial imbalances in powerful baseline prognostic variables with the potential to confound treatment assignment meaningfully, we will perform a sensitivity analysis using a logistic regression model to adjust for these factors. If more than two factors need to be adjusted for, we will summarize them using propensity scores [Rosenbaum 1983], then use a logistic model to adjust for the scores as a three-knot cubic spline, requiring two basis functions, so that the conservative rule of thumb of approximately 10 events per variable is observed [Vittinghoff 2006].

3. *Inverse weighting to deal with indeterminate cause of death and missing vital status.* In the primary analysis, participants with indeterminate cause of death or missing vital status will be assumed not to have had a primary study event. In two secondary analyses, we will restrict the analysis to deceased participants with determinate cause of death and those known to be alive, weighting these observations so that their baseline correlates of the primary outcome are representative of the entire randomized cohort. To do this, we will develop two logistic models: the first for having determinate cause of death among all patients known to have died, and the second for having known vital status among all participants. Weights will be calculated as the inverse of the product of the fitted probabilities from these two models, after assigning a fitted probability of 1 from the first model for patients known to be alive. Variables in each model will be selected, without regard to the primary outcome, from a list of known correlates of the primary study outcome, as specified by Drs. Olgin, Lee, and Pletcher. To deal with missing values of the candidate variables in the *a priori* list, multiple imputation will be used, followed by averaging of the weights obtained from each of ten completed datasets. Two versions of this sensitivity analysis will be conducted, the first excluding and the second using information from the vest in

determining vital status. The weighted analyses will use procedures properly accounting for the slightly smaller sample size available for analysis.

B.2. Heterogeneity of treatment effects

o *By randomization stratum.* We will use a logistic model to assess heterogeneity of the treatment effect across the 6 randomization strata jointly defined by EF, PCI, and CABG, as well as across the 2 strata defined by EF and the 3 strata defined by PCI and CABG. Nominal differences across strata will be conservatively interpreted in the light of tests for interaction between treatment and stratum, using a Bonferroni-corrected two-sided alpha of 0.05/3=0.0167. In additional exploratory analysis, we will assess modification of the ITT treatment effect by drugs, NYHA class, BMI, gender, and compliance

B.3. Treatment effects on secondary endpoints

o *Total mortality, revascularization, ICD implantation*. Treatment effects on these binary secondary endpoints will be analyzed using chi-square tests, as proposed for the primary analysis. Logistic regression will be used to adjust for baseline imbalances as needed.

o *Re-infarctions and hospitalizations*.Treatment effects on these potentially recurring outcomes will be analyzed using the Anderson-Gill extension of the Cox model for recurrent events, with robust standard errors [Therneau 2000], to account for potential clustering of recurrent outcomes within participants.

o *Vest-related symptoms*. Fisher's exact tests will be used to compare frequency of potentially vest-related symptoms currently tabulated in the DSMB report, including fatigue, back pain, trouble sleeping, and upper body rash and itching.

B.4. Exploratory analysis of compliance

Factors associated with compliance with the VEST will be examined in an exploratory, hypothesis- generating analysis focusing on seasonality, site, geographic region, body mass index (BMI), time on study, baseline EF, as well as age, gender, race/ethnicity, education, marital and employment status, NYHA Class, and length of hospital stay. The analysis will use two-part models for repeated daily compliance measures, the first a GEE logistic model for any use of the VEST, and the second a GEE linear model for hours of use, transformed as necessary to meet normality assumptions, for patient-days where any use is detected. Inference for the combined effects of each proposed covariate on both elements of compliance (any use and hours of use among users) will be implemented using the seemingly unrelated estimation strategy. [Weesie, 1999]

C. References

- Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects Biometrika. 1983;70:41-50.
- Therneau T, Grambsch P. Modeling survival data: extending the Cox model. New York: Springer; 2000.
- Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol. 2006:165(6):710-8.
- Weesie, J. 1999. sg121: Seemingly unrelated estimation and the cluster-adjusted sandwich estimator. Stata Technical Bulletin 52: 34–47. Reprinted in Stata Technical Bulletin Reprints, vol. 9, pp. 231–248. College Station, TX: Stata Press.