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Short Title: HF OPT Study

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HEART FAILURE OPTIMIZATION STUDY

Short Title:	**HF Opt Study**
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Study Device:	**ZOLL LifeVest®**
Protocol Number:	**90D0109**
IDE Number:	**NA**
Version Date:	**Rev D, last modified March 9, 2020**

I have read and understand the information in the protocol and I understand my requirements for executing the protocol based on sound knowledge of GCP and ICH Guideline for Good Clinical Practice (E6).

PRINTED NAME OF INVESTIGATOR	SITE NUMBER
INVESTIGATOR SIGNATURE	DATE
SPONSOR REPRESENTATIVE	11-Mar-2020 DATE

Table of Contents

STUDY SUMMARY **1**

1 INTRODUCTION **2**

1.1 Background 2
1.2 Preclinical Data 3
1.3 Clinical Data to Date 3
1.4 Study Device 4

2 STUDY OBJECTIVES **5**

2.1 Primary Objective(s) 5
2.2 Secondary Objective(s) 5
2.3 Safety Objective(s) 6
2.4 Additional Objective(s) 6

3 STUDY DESIGN **6**

3.1 General Design 6
3.2 Primary Study Endpoints 8
3.3 Secondary Study Endpoints 8
3.4 Safety Endpoints 9

4 STUDY SUBJECT **10**

4.1 Inclusion Criteria 10
4.2 Exclusion Criteria 10

5 STUDY ENROLLMENT PLAN **11**

5.1 Enrollment Strategy 11
5.2 Study Size 11
5.3 Enrollment Period 11
5.4 Early Withdrawal of Subjects 11

6 STUDY PROCEDURES **12**

6.1 Subject Recruitment and Screening 12
6.2 Scheduled Visits 12
6.3 Unscheduled Visits 14
6.4 Long-term Clinical Outcome Assessment 15
6.5 Study Procedures Flowchart (or Table) 15
6.6 Blinding and Unblinding of Study 16

7 STUDY DEVICE MANAGEMENT **16**

7.1 Subject Compliance Monitoring 16
7.2 Managing WCD Therapy 17
7.3 Dispensing, Storage and Return 17
7.4 Device Malfunction or Defect 17

8 STATISTICAL PLAN **17**

8.1 Sample Size and Power Calculation 17
8.2 Randomization Scheme 20
8.3 Endpoint Assessment 20
8.4 Statistical Methods 21
8.5 Additional Statistical Analysis 21
8.6 Handling Missing Data 22

8.7 FUTILITY ANALYSIS 22
9 HEALTH ECONOMIC EVALUATION 22
10 SAFETY AND ADVERSE DEVICE EFFECTS 22
10.1 DEFINITIONS 22
10.2 RECORDING AND REPORTING OF ADVERSE DEVICE EFFECTS 23
10.3 PROTOCOL DEVIATIONS 24
11 ADMINISTRATIVE RESPONSIBILITIES 25
11.1 SPONSOR 25
11.2 INVESTIGATORS 25
11.3 DATA COORDINATION CENTER (DCC) 25
11.4 STEERING COMMITTEE 25
11.5 DATA SAFETY MONITORING BOARD (DSMB) 26
12 DATA COLLECTION AND MANAGEMENT PLAN 26
12.1 DATA COLLECTION 26
12.2 DATA HANDLING AND RECORD KEEPING 26
12.3 DATA TRANSMISSION FROM SPONSOR 27
12.4 STUDY MONITORING PLAN 28
13 RISKS AND BENEFITS 28
14 ETHICAL CONSIDERATIONS 28
14.1 SUBJECT CONSENT AND CONFIDENTIALITY 29
14.2 SUBJECT FINANCIAL RESPONSIBILITY AND STIPENDS 29
15 PUBLICATION PLAN 29
15.1 AUTHORSHIP 29
15.2 DATA OWNERSHIP 30
16 INTELLECTUAL PROPERTY AND PATENTS 30
17 LIST OF ABBREVIATIONS 30
18 BIBLIOGRAPHY 31
19 REFERENCE DOCUMENTS 32

Study Summary

Title	Heart Failure Optimization Study
Short Title	HF Opt Study
ZOLL Protocol Number	90D0109
Study Design	Prospective observational study
Study Duration	Approximately 60 months
Study Center(s)	Multi-center, Thirty to eighty sites, in US and Europe
Primary Objective(s)	Observe the rate of recovery of ventricular function (EF>35%) between 90 and 180 days in newly diagnosed HF with reduced EF patients.
Study Population	Patients who were prescribed the wearable cardioverter defibrillator (WCD) ≤ 10 days post-discharge after hospitalization for a primary reason of new onset HF (≤30 days since first HF hospitalization), with ischemic or nonischemic cardiomyopathy, and have already used a WCD for 90 ± 14 days. For the first 90 days of WCD use, patients will be enrolled in a pre-study registry.
Intervention	An FDA-approved, CE marked WCD will be prescribed for up to 6 months of use after hospital discharge, with the option for longer use under physician discretion
Study Size	Up to 600 for the study, up to 1400 for the pre-study registry
Reference therapy	NA

1 Introduction

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonization ICHE6), the Code of Federal Regulations Title 21 parts 803 and 812, and other applicable government regulations and Institutional research policies and procedures.

1.1 Background

1.1.1 Sudden Cardiac Death in Heart Failure

Sudden cardiac death (SCD) is usually defined as death from a cardiac etiology within an hour of the onset of symptoms in a person who otherwise appeared in a stable clinical state. These deaths are often attributed to a cardiac arrhythmia, of which ventricular fibrillation is the most common. In the United States, SCD is the leading cause of death accounting for nearly 350,000 deaths per year or approximately 1,000 deaths per day.[1,2] Although a preexisting heart condition may not be present, patients known to have heart failure (HF) have been shown to have a higher risk of SCD. Among patients with HF, those with ventricular dysfunction as evidenced by a lower left ventricular ejection fraction (LVEF) have a particularly high risk of SCD.

Over one million hospital admissions for acutely decompensated heart failure occur annually in the USA and one in nine death certificates list heart failure as a related cause.[2] Within the Veterans Affairs Health Care System, mortality after discharge has declined but remains significant (over 10% at 90 days post-discharge in 2006), and re-admission rates have trended higher (over 6% at 30 days in 2006).[3] Similar data has been reported among Medicare recipients.[4] Sudden cardiac death may account for half of the cardiovascular mortality experienced.[5,6]

1.1.2 Treatment of SCD in Heart Failure Patients

Implantable cardioverter-defibrillators (ICDs) have been shown to reduce both arrhythmic and total mortality in stable heart failure patients[7] with significant ventricular dysfunction. However, according to the ACCF/AHA guidelines ICDs for primary prevention HF patients should not be considered until optimal guideline-directed medical therapy (GDMT) has been achieved, with a minimum of 3 to 6 months of appropriate medical therapy[8,9]. Since stability in heart failure is

[1] American Heart Association, Textbook of Advanced Cardiac Life Support.

[2] Mozaffarian et al., "Heart Disease and Stroke Statistics—2016 Update," Circulation 2016; 133(4):e38-e360.

[3] Heidenreich et al., "Divergent Trends in Survival and Readmission Following a Hospitalization for Heart Failure in the Veterans Affairs Health Care System 2002 to 2006," JACC 2010; 56;362-368.

[4] Bueno, "Trends in Length of Stay and Short-term Outcomes Among Medicare Patients Hospitalized for Heart Failure, 1993-2006," JAMA 2010; 303(21):2141-2147.

[5] Zannad et al., "Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms," N Engl J Med 2010; online November 14, 2010.

[6] Mozaffarian et al., "Prediction of Mode of Death in Heart Failure The Seattle Heart Failure Model," Circulation 2007; 116:392-398.

[7] Bardy et al., "Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure," N Engl J Med 2005; 352:225-37.

[8] Yancy et al, "2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines," Circulation 2013; 128:e240-e327.

[9] Ponikowski et al, "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure," European Heart Journal 2016; published online.

frequently not attainable within 90 days after discharge, ICD implantation during this period of high risk commonly does not meet GDMT guideline standards.

Another method of SCA risk protection frequently used after HF hospitalization is the wearable defibrillator (WCD).[10] WCDs have been commercially approved for use by the FDA and CE marked for Europe since 2001. Since a WCD is non-invasive and can easily be removed, it makes an ideal device for protecting HF patients when SCD risk is high yet recovery is still possible. After medications have been titrated into appropriate doses and the EF has been given time to recover, the WCD can be removed and an assessment for ICD implantation due to permanent SCD risk can be performed.

1.2 Preclinical Data

NA

1.3 Clinical Data to Date

Previous clinical data reveals that the following questions remain controversial subjects in newly diagnosed HF patients:

1) How long does it take to achieve optimal medical therapy?, and therefore,

2) When to implant an ICD in a newly diagnosed patient?, and

3) How often and when to measure EF recovery?

Titration to therapeutic levels is generally not achieved within three months of initiation[11,12] for some drugs known to improve ventricular dysfunction, and improvements in heart failure symptoms and ventricular dysfunction may occur after optimization of medical therapy over time.

A recent retrospective study of Medicare patients linked to the National Cardiovascular Data ICD Registry showed a very low rate of guideline-directed medical therapy being achieved in the 90 days before ICD implantation[13]. Only 61.1% had filled their prescriptions for a HF beta-blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at least once during the 90 days before ICD implantation, and only 28.3% had a supply for ≥80% of the 90 days. Interestingly, those with the shortest duration of HF and most recent evaluation of EF were the least likely to receive guideline-directed medical therapy. Death within one year occurred more frequently in those patients not receiving any guideline-directed medical therapy even after adjusting for patient characteristics, HF severity, and comorbidities.

Although EF is typically measured in the beginning, and usually at some follow-up period, it is unknown how often EF should be measured and what “recovery” of LV dysfunction means in terms of outcomes. The IMAC-2 study looked at myocardial recovery in newly diagnosed NICM

[10] Feldman et al., “Use of a Wearable Defibrillator in Terminating Tachyarrhythmias in Patients at High Risk for Sudden Death: Results of WEARIT/BIROAD,” PACE 2003; 27:4-9.

[11] Fonarow et al., “Dosing of Beta-Blocker Therapy Before, During, and After Hospitalization for Heart Failure,” Am J Cardiol 2008; 102:1524–1529.

[12] Gustafsson et al., “Treatment with beta-blockers in nurse-led heart failure clinics: Titration efficacy and predictors of failure,” Euro J of Heart Failure 2007; 9:910–916.

[13] Roth et al, “Use of Guideline-Directed Medications for Heart Failure Before Cardioverter-Defibrillator Implantation,” JACC 2016; 67:1062-9.

patients with EF ≤40%. They found that 40% of patients had an EF≥45% at 6 months, and 25% had an EF≥50%[14]. Among DEFINITE trial subjects with follow-up EF measurements, 32% improved EF over 35% during the first two years of the trial despite enrollment criteria of EF ≤35% and "stable" HF for at least 30 days[15]. They also found that patients with LVEF improvement had a decreased risk of total mortality, although no reduction in arrhythmic events. In contrast to the IMAC-2 study, the DEFINITE study excluded reversible cardiomyopathies, which may explain the lower recovery rate seen in DEFINITE patients.

1.4 Study Device

1.4.1 Wearable Cardioverter Defibrillator (WCD)

To date, several studies have demonstrated the impact WCD's have had in successfully resuscitating patients from ventricular tachyarrhythmias. In fact, the first shock termination success of 98% for sustained ventricular tachyarrhythmias and the 94% survival to conscious emergency room arrival is far superior to any other form of outpatient resuscitation. The highest rates of survival from SCA secondary to ventricular tachyarrhythmias (53%) are reported to be in casinos[16] owing to the rapid defibrillation afforded by witnessing most patient collapses (surveillance is constant) and close availability of defibrillators. Since no witness is required for a WCD to detect and defibrillate, when a WCD is worn it provides outpatient defibrillation faster than that afforded from constant, close human observation.

Wearable defibrillators have shown great success in treating SCA[17,18,19]. However, the data confirming the overall impact of WCD by allowing for LVEF recovery is limited[20]. As the device is being used routinely in some centers for selected high-risk HF patients after discharge, a prospective study is warranted to confirm that the WCD benefits these patients, both in terms of SCD protection and by allowing for ICD deferment until LV recovery may occur.

1.4.2 WCD Technical Details

The LifeVest® wearable defibrillator is composed of four dry, non-adhesive capacitive electrodes and three dry-to-wet non-adhesive defibrillation electrodes incorporated into a chest strap assembly, along with a 1.7 lbs defibrillator unit carried on a waist belt. The monitoring electrodes are positioned circumferentially around the chest and held in place by about 1 to 1.5 lbs of tension. The defibrillation electrodes are positioned for apex-posterior defibrillation. If an arrhythmia is detected, an escalating alarm sequence starts, including a vibration against the skin, audible tones, and a voice cautioning bystanders of an impending shock. Patients are trained to hold a pair of response buttons during these alarms. Responding acts as a test of consciousness: if no

[14] McNamara et al, "Clinical and Demographic Predictors of Outcomes in Recent Onset Dilated Cardiomyopathy," JACC 2011;58(11):1112-8.

[15] Schliamser et al, "Significance of follow-up left ventricular ejection fraction measurements in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE), Heart Rhythm, 2013; 10(6):838-846.

[16] Valenzuela et al., "Outcomes of Rapid Defibrillation by Security Officers after Cardiac Arrest in Casinos." N Engl J Med, 2000; 343:1206-9.

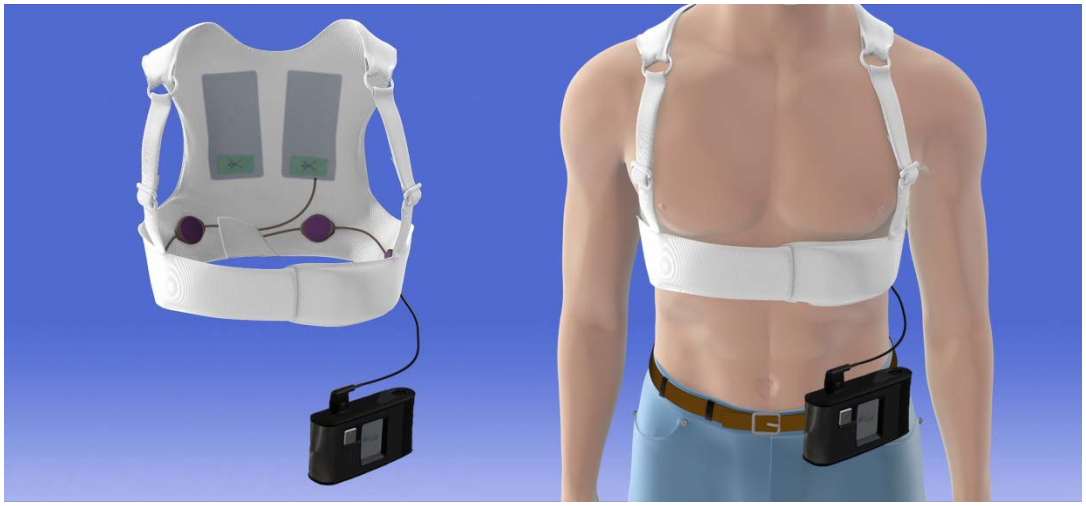
[17] Klein et al., "Bridging a Temporary High Risk of Sudden Arrhythmic Death. Experience with the Wearable Cardioverter Defibrillator (WCD)." PACE 2010; 33(3):353-67.

[18] Chung et al., "Aggregate National Experience With the Wearable Cardioverter-Defibrillator." JACC 2010; 56(3):194–203.

[19] Epstein et al, "Wearable Cardioverter-Defibrillator Use in Patients Perceived to Be at High Risk Early Post-Myocardial Infarction." JACC 2013; 62(21):2000-7.

[20] Kao et al, "Wearable defibrillator use in heart failure (WIF):results of a prospective registry." BMC Cardiovascular Disorders 2012; 12:123.

response occurs, the device extrudes gel from the defibrillation electrodes and delivers up to five 150-Joule biphasic shocks.



2 Study Objectives

2.1 Primary Objective(s)

The primary objective of this study is to observe the rate of recovery of ventricular function (EF>35%) between 90 and 180 days in newly diagnosed HF with reduced EF patients who were prescribed the WCD while being initiated on their HF medications. This will be measured from EF closest to before hospital discharge, then at 90, 180 and 360-days after WCD start, regardless of continued WCD use, prior EF improvement, or ICD implantation. While approximately one-third of the patients will likely experience EF recovery in the first 90 days, we hypothesize that an additional 5-10% of patients will experience EF improvement between 90 and 180 days as GDMT is achieved. This would be considered clinically significant in terms of the potentially avoided ICD implantations. Outcomes will be tracked and reported for three pre-specified groups based on assessment of SCD risk at 90 days of WCD use:

1) Patient improved (EF >35%), SCD risk deemed to be negligible. These patients are expected to end WCD use and not receive an ICD.
2) Patient improved EF from start of WCD use (a positive change of at least 5 percentage points in EF), or has a borderline EF of 30-35%, but still has continued SCD risk (EF ≤ 35%). These patients are expected to continue to use the WCD for an additional 3 months.
3) Patient not improved from start of WCD use (no change or worsening of EF), EF<30% and has continued high SCD risk. Those on GDMT are expected to be evaluated for an ICD. Those not yet on GDMT may continue the WCD for an additional 90 days.

2.2 Secondary Objective(s)

The specific secondary objectives are to:

2.2.1 Observe the incidence and etiology of SCA and all sustained VT/VF arrhythmias during WCD use.

2.2.2 Observe the incidence of other arrhythmias during WCD use, such as asystole and supra-ventricular arrhythmias that are recorded by the device.

2.2.3 Collect ICD treatment data for those who receive an ICD, and evaluate for appropriateness.

2.2.4 Observe the effectiveness of the wearable defibrillator worn by this population in treating ventricular arrhythmias. Clinical outcomes data from any defibrillation or cardiac event will be collected, including device data on appropriate arrhythmia detection and shock delivery.

2.2.5 Evaluate the effect of wearable defibrillators on 90,180, 270, and 360-day mortality following WCD start in HF patients. Assessment of survival will be made at these time points for those entered into the study. A mortality review will be conducted to group all deaths as cardiac or non-cardiac, and sudden or non-sudden.

2.2.6 Collect economic and healthcare utilization data on all patients.

2.3 Safety Objective(s)

The safety objectives will be to compare complications from extended use of the WCD with those of the ICD during the study timeframe.

2.4 Additional Objective(s)

Echocardiogram core lab determinations will be used to verify local estimates of EF and may be used in secondary analyses of the study data.

3 Study Design

3.1 General Design

This study is designed as a multi-center prospective observational study of newly diagnosed HF with reduced EF patients to test the hypothesis that additional EF recovery occurs between 90 and 180 days as GDMT is achieved. Although the study doesn't start until day 90, all eligible, consenting patients will be entered into a registry at the start of WCD use. The pre-study registry will allow us to collect early (90 day) outcomes and data in those patients who are likely to be eligible for the study at day 90, or are eligible, but refuse the study at day 90.

3.1.1 Randomization
Because WCD's have been shown to be very effective at treating potentially lethal ventricular tachyarrhythmias and are already FDA-approved and CE marked for use in the study population, randomization will not be done. This observational study will gather information on improvement in EF with medical therapy, WCD use, sudden cardiac arrest event rates, and outcomes within a select group believed to be at high risk for SCD.

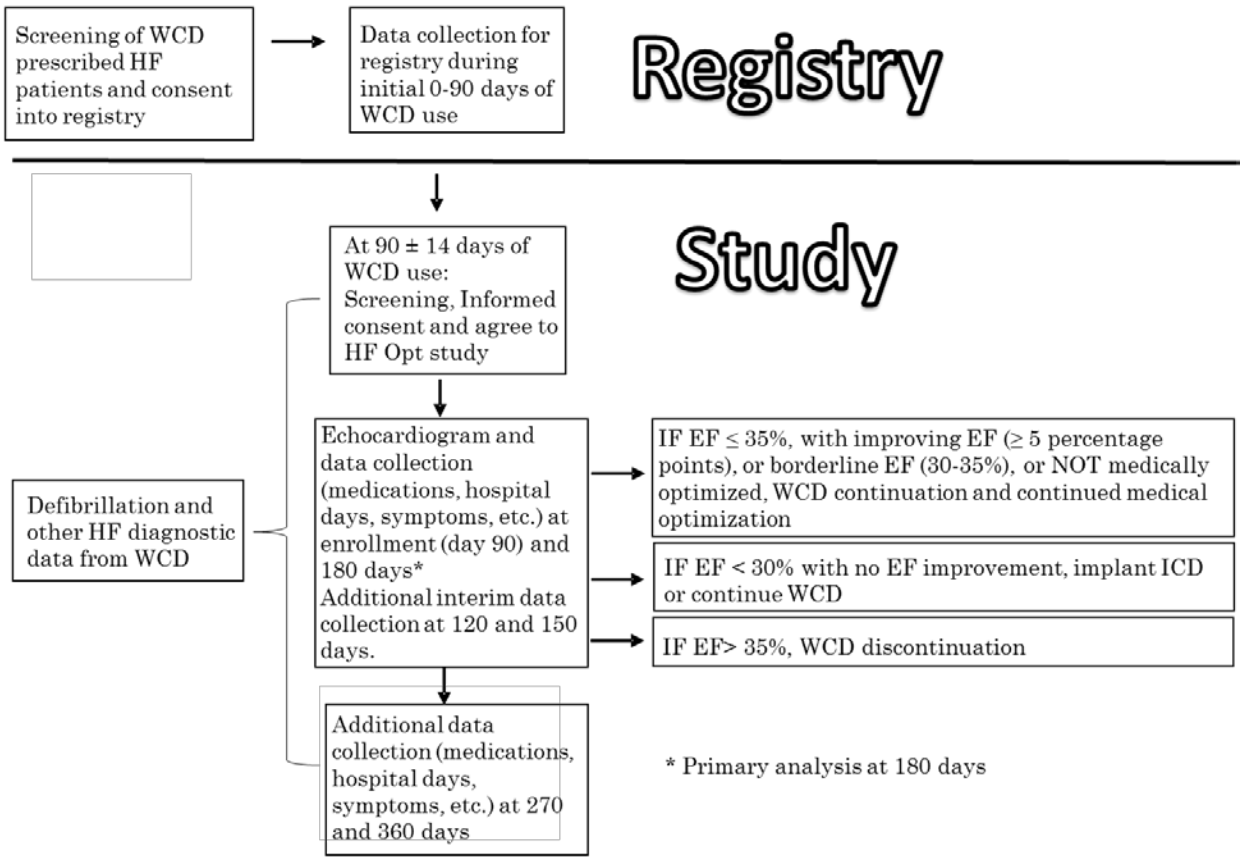
3.1.2 Blinding

Investigators and treating physicians will not be blinded during the study to any WCD device records that are generally available for physicians to access. This includes ECG and compliance data as recorded by the WCD during patient use.

3.1.3 Expected Duration of Study Participation

The anticipated length of active study participation is 12 months from the start of WCD use.

3.1.4 Schematic diagram of study design



3.1.5 Expected Duration of WCD use

WCD use is expected to continue for an additional 90 days post study enrollment (180 days total) for patients with EF ≤ 35% and not on GDMT. In the event of an aborted SCA or symptomatic sustained ventricular tachycardia/fibrillation (VT/VF), patients may be implanted with an ICD.

Patients who receive an ICD early (prior to reaching GDMT or not otherwise having an indication for an ICD) versus continuing WCD as described by the protocol will not be considered withdrawn from the study, and will continue to be followed.

Patients who refuse an ICD or WCD continuation as described by the protocol (EF ≤ 35%) will not be considered withdrawn from the study, and will continue to be followed.

3.2 Primary Study Endpoints

The primary objective of this study is to observe the rate of recovery of ventricular function (EF>35%) between 90 and 180 days in newly diagnosed HF with reduced EF patients being treated with GDMT. The primary endpoints that will be used to support the primary objective are 1) the degree to which GDMT has been achieved, and 2) rates of EF recovery at pre-specified time-points post WCD start.

3.2.1 GDMT

Medications and self-reported adherence to taking those medications as prescribed will be recorded from chart review and patient interview if necessary at day 90, 120, 150, 180, 270, and 360. Medications will also be recorded at the start and end of WCD use.

GDMT will be defined by use of the minimum ACCF/AHA/HFSA/ESC guideline-recommended therapies, such as HF treatments with any renin-angiotensin inhibitor (angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) if ACE-I is not tolerated), and reaching target evidence-based doses (or the maximally tolerated levels) of beta-blockers[8,9]. Mineralocorticoid/aldosterone receptor antagonists (MRAs) are to be included along with ACE-I and beta-blocker treatments, and should be titrated to reach evidence-based doses (or the maximally tolerated levels). Further extension of medications according to current guidelines, including I_f-channel inhibitor or angiotensin receptor neprilysin inhibitor will be considered additional HF therapy left to the discretion of the treating physician, but will not be required to define “optimal medical therapy”.

3.2.2 LVEF recovery

To support our primary hypothesis that an additional 5% of patients will experience EF improvement between 90-180 days, EF measurement for all patients at 90 (±14), 180 (±14) and 360 (±14)-days after WCD start will be requested and recorded. For this study, EF>35% will be considered as EF improved.

3.2.2.1 Echocardiographic assessment of LVEF is most common. Nevertheless, other imaging modalities (MUGA, MRI) may be used to document LVEF at day 0. Although there are likely to be differences in EF assessment among enrolling sites and practices, these differences are not expected to affect the outcome of the trial. At a minimum, we will request a 2-D, M-mode echo at the scheduled time-points.

3.2.2.2 Echocardiogram core lab verification. EF is commonly estimated by echocardiogram. Several studies have shown EF measurement to have a wide range of variability that can be observer dependent. Study echocardiograms will be sent to a core lab for a uniform determination of the EF. The core lab determinations will be used to verify local estimates of EF and may be used in secondary analyses of the study data

3.3 Secondary Study Endpoints

The secondary endpoints are observational and include documentation of any SCA/SCDs, including any treatments by the WCD or ICD, any untreated sustained ventricular arrhythmias that are recorded by the WCD, and the mortality following discharge in HF patients. We will also collect economic and healthcare utilization data on all patients.

3.3.1 SCA/SCD, Sustained Ventricular Arrhythmias, and Mortality

3.3.1.1 “Sudden Cardiac Death” will be defined as an unexpected, non-traumatic, non-self-inflicted fatality in otherwise stable subjects who die within one hour of the onset of the terminal symptoms. Subjects dying more than one hour after a sudden cardiac arrest (SCA) from a ventricular arrhythmia will be designed as non-sudden death due to ventricular arrhythmia. For unwitnessed deaths participants will meet the definition of sudden cardiac 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. Autopsy results may be used when available.

For the mortality analysis, all deaths will be classified by the site investigator as cardiac or non-cardiac, and sudden or non-sudden.

3.3.1.2 “Appropriate detection” will be defined as a device alarm/detection during a ventricular tachyarrhythmia.

3.3.1.3 “Sustained ventricular arrhythmia” will be defined as any WCD-recorded appropriate detection with ≥ 30 seconds of uninterrupted VT/VF.

3.3.1.4 “Appropriate treatment” will be defined as a therapy shock or anti-tachycardia pacing (ATP) given during a ventricular tachyarrhythmia.

3.3.1.5 “Inappropriate treatment” will be defined as a therapy shock and/or ATP (for ICD recipients) delivered in the absence of an appropriate detection.

3.3.1.6 “Other treatment” will be defined as a therapy shock delivered during an appropriate detection but on a section of the recording not showing a ventricular arrhythmia.

3.3.2 Effectiveness of the wearable defibrillator in treating ventricular arrhythmias

Clinical outcomes and device data from any defibrillation or cardiac event will be reviewed for success as defined by appropriate detection and defibrillation, conversion out of the detected ventricular arrhythmia, and consciousness when medically evaluated after treatment.

3.3.3 Incidence of other WCD recorded arrhythmias, such as asystole and supra-ventricular arrhythmias.

3.3.4 Economic and healthcare utilization data on all patients

Information (days, reasons) on any hospitalizations, emergency room visits, observation stays, urgent care visits, other physician office visits, and stays at skilled nursing facilities.

3.4 Safety Endpoints

The safety objectives will be to compare complications from extended use of the WCD with those of the ICD during the study timeframe.

3.4.1 Complication data from ICDs for those who receive an ICD, including inappropriate interventions or other ICD-related complications that may lead to hospitalization or death.

3.4.2 Complication data from WCDs, including inappropriate shocks or other WCD-related complications that may lead to hospitalization or death.

4 Study Subject

4.1 Inclusion Criteria

The population for this study will be patients who had an ejection fraction (EF) ≤ 35% following hospitalization for newly diagnosed HF, and who have already been using a WCD for 90 days. Prior to 90 days, eligible patients will be enrolled into a registry. Registry patients will be enrolled during the first 30 days of WCD use.

All of the following must be true for enrollment into the registry (day 0 – 90 of WCD use):

4.1.1 Patients (≥18 years old) who were prescribed the WCD ≤ 10 days post-discharge after hospitalization for a primary reason of newly diagnosed HF with reduced EF (≤30 days since first HF hospitalization), with ischemic or nonischemic cardiomyopathy, and have used the WCD for no more than 30 days.

4.1.2 Patients who had an EF ≤ 35% during index hospitalization.

All of the following must be true for enrollment into the study (day 90 ± 14):

4.1.3 Patients (≥18 years old) who were prescribed the WCD ≤ 10 days post-discharge after hospitalization for a primary reason of newly diagnosed HF with reduced EF (≤30 days since first HF hospitalization), with ischemic or nonischemic cardiomyopathy, and either 1) have already used a WCD for 90 ± 14 days or 2) were enrolled in the registry after 01-March-2019 and received an ICD prior to 90 days of WCD use.

4.1.4 Patients who had an EF ≤ 35% during index hospitalization. Of note, EF at 90 ± 14 days post-hospitalization does not need to be low to be included in the study.

4.2 Exclusion Criteria

The exclusion criteria for enrollment into the registry (day 0-90) are: (none can be true)

4.2.1 Patients under 18 years old.

4.2.2 Patients who have an active unipolar pacemaker.

4.2.3 Patients with a physical or mental condition that could impair their ability to properly interact with the device.

4.2.4 Patients currently participating in an interventional clinical study.

4.2.5 Patients with any skin condition that would prevent wearing the device.

4.2.6 Patients with an advanced directive prohibiting resuscitation.

The exclusion criteria for enrollment into the study (day 90 ± 14) are: (none can be true)

4.2.7 Patients under 18 years old.

4.2.8 Patients who have an active unipolar pacemaker.

4.2.9 Patients with a physical or mental condition that could impair their ability to properly interact with the device.

4.2.10 Patients currently participating in an interventional clinical study.

4.2.11 Patients with any skin condition that would prevent wearing the device.

4.2.12 Patients with an advanced directive prohibiting resuscitation.

4.2.13 Patients who have a QRS duration of ≥135 ms and are planned for cardiac resynchronization therapy during the study duration.

4.2.14 Patients with recent myocardial infarction or coronary revascularization (since start of WCD wear; i.e. 0-90 days of WCD wear).

5 Study Enrollment Plan

5.1 Enrollment Strategy

Investigators and sites will be identified based upon site-initiated interest in the study, sites that have adequate HF patient volumes, and through sponsor-identified research sites that are currently high prescribers of the WCD for HF patients. Some investigators may be identified through an Institutional Review Board (IRB) database service.

Patient enrollment strategies may be targeted at both the investigator and the patient as a way to engage all interested parties and provide informational materials for the study. Strategies may include patient and/or investigator focus groups, educational lectures, web sites, or flyers, or study coordinator brochures to assist in the recruitment and screening process.

5.2 Study Size

Up to 1400 subjects will be enrolled into the pre-study registry, and up to 600 may be enrolled in the study portion. Thirty to eighty sites will enroll patients into the study. Sites will initially be located in the United States and Germany, but may be expanded to other European countries. Individual sites will only be allowed to enroll up to 140 patients (or 10% of the total population).

5.3 Enrollment Period

This study is expected to finish enrollment within 48 months after the start of enrollment.

5.4 Early Withdrawal of Subjects

5.4.1 When and How to Withdraw Subjects

All patients enrolled into the study can withdraw at any time regardless of the reason. Patients may withdraw consent for use of data and exit the study at any time without prejudice to further treatment.

Patients who receive an ICD versus continuing WCD as described by the protocol will not be considered withdrawn from the study, and will continue to be followed.

Patients who refuse an ICD or WCD continuation as described by the protocol will not be considered withdrawn from the study, and will continue to be followed.

5.4.2 Data Collection and Follow-up for Withdrawn Subjects

When a subject withdraws from participating in the study, this will be documented, and the already collected data will remain part of the study and will be used in data analysis. The reason for withdrawal from the study will also be documented, if known. If the patient agrees, a follow-up phone call to assess mortality only may still be made.

In the case of patients who are lost to follow-up, all pre-existing study data on the patient will still be used.

6 Study Procedures

6.1 Subject Recruitment and Screening

6.1.1 Subject screening for WCD registry and study

Patients will initially be screened from the prescribed WCD patients and enrolled into the pre-study registry. At 90 ± 14 of WCD use, study subjects will be identified and screened from the clinical site's pre-study registry participants. The sponsor may also assist in the screening process by maintaining a current list of WCD prescribed patients to be screened for the registry by each site. Registry participation is complete when the patient enters the HF Opt study, or ends WCD use.

6.1.2 Subject recruitment into study

Once the site has determined that the patient meets the inclusion/exclusion criteria, the patient will be scheduled for their 90 ± 14 day follow-up visit and echocardiogram, at which point they may be approached by the study staff for verification of inclusion/exclusion and for consent into the study.

6.1.3 Steps for screening and consent of patients:

1) A chart review of patients prescribed the WCD (in the last 30 days) after hospitalization for HF will be used to evaluate patients for enrollment into the pre-study registry.

2) Potentially eligible patients from the registry will be scheduled for a 90 ± 14 day follow-up visit and echocardiogram.

3) If eligible, at the 90 ± 14 day follow-up visit, patients will be consented and enrolled into the study.

6.2 Scheduled Visits

6.2.1 Clinical and EF reassessment at pre-specified timepoints

6.2.1.1 Upon enrollment into the pre-study registry, baseline clinical data will be recorded from chart review and patient interview if necessary.

6.2.1.2 After enrollment into the study, additional clinical data will be recorded from chart review and patient interview if necessary at 90, 120, 150, 180, 270 and 360 days post WCD start. This data will include medications, ER visits, HF hospitalizations, survival, ICD placement, and last known clinical status.

A subset of sites will also collect quality of life (QOL), patient reported data at baseline (registry enrollment), 90 (±14), and 180 (±14) days of WCD use. QOL data from 350 enrolled patients (from US and Europe) will be collected using the Kansas City Cardiomyopathy Questionnaire (KCCQ-12)[21].

6.2.1.3 EF measurement at 90 (±14), 180 (±14) and 360 (±14)-days post WCD start will be requested and recorded. Any additional EF measurements taken at the end of WCD use will be collected as well, if not at one of these already pre-specified timepoints (see 6.3.1.2).

6.2.1.3.1 Echocardiographic assessment of LVEF is most common. Nevertheless, other imaging modalities (MUGA, MRI) may be used to document LVEF at day 0. Although there are likely to be differences in EF assessment among enrolling sites and practices, these differences are not expected to affect the outcome of the trial. At a minimum, we will request a 2-D echo at the scheduled time-points.

The following scheduled visit is for all registry patients:

6.2.2 Visit post-index hospitalization (day 0 - 30 from WCD start)
- 6.2.2.1 Inclusion/exclusion will be verified.
- 6.2.2.2 Informed Consent for registry will be obtained.
- 6.2.2.3 Clinical history data will be collected, including current Echo and ECG data.
- 6.2.2.4 Medication usage will be collected
- 6.2.2.5 QOL data will be collected (subset of patients only)

The following scheduled visits are for all study patients, regardless of ongoing WCD use, and include:

6.2.3 Visit 1 - Enrollment (day 90 ± 14 from WCD start)

- 6.2.3.1 Inclusion/exclusion will be verified.
- 6.2.3.2 Informed Consent will be obtained.
- 6.2.3.3 Clinical data will be collected, including current Echo and ECG data.
- 6.2.3.4 Medication usage will be collected and any adjustments made to achieve GDMT.

- 6.2.3.5 QOL data will be collected (subset of sites only)

For patients who will be continuing WCD use only:

- 6.2.3.5 Medical orders and dispensing of the WCD will follow current commercial procedures.

[21] Spertus and Jones. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes. 2015;8:00-00.

6.2.4 Patient interviews through follow-up phone calls or office visits (days 120 ± 14 and 150 ± 14 from WCD start)
- 6.2.4.1 Clinical data will be collected
- 6.2.4.2 Medication changes will be collected
- 6.2.4.3 Device information, adverse events, and cardiac event information will be collected as needed

6.2.5 Visit 2 (day 180 ± 14 from WCD start)
- 6.2.5.1 Clinical data will be collected, including current Echo.
- 6.2.5.2 Medication changes will be collected.
- 6.2.5.3 Device information, adverse events, and cardiac event information will be collected.
- 6.2.5.4 If patient has recently ended the study, or WCD use, reasons will be collected.
- 6.2.5.5 QOL data will be collected (subset of patients only)

6.2.6 Patient interview through follow-up phone calls or office visits (day 270 ± 14 from WCD start)
- 6.2.6.1 Clinical data will be collected.
- 6.2.6.2 Medication changes will be collected.
- 6.2.6.3 Device information, adverse events, and cardiac event information will be collected.
- 6.2.6.4 If patient has recently ended the study, or WCD use, reasons will be collected.

6.2.7 Visit 3 (day 360 ± 14 from WCD start)
- 6.2.7.1 Clinical data will be collected, including current Echo.
- 6.2.7.2 Medication changes will be collected.
- 6.2.7.3 Device information, adverse events, and cardiac event information will be collected.
- 6.2.7.4 If patient has recently ended the study, or WCD use, reasons will be collected.

6.3 Unscheduled Visits

Unscheduled visits for registry or study patients may include:

6.3.1 Resuscitation from SCA event, death, inappropriate shock, and unanticipated end of WCD use or study completion (immediately following notification of occurrence)
- 6.3.1.1 In the event of a WCD recording that indicates shock, sustained VT/VF >30 seconds with no shock, or asystole (<10 BPM), sites will be notified from ZOLL of the occurrence, and ECG strips will be sent.
- 6.3.1.2 Clinical data will be collected, including any additional EF measurements that were taken at the end of WCD use.
- 6.3.1.3 Device information, adverse events, and cardiac event information will be collected.
- 6.3.1.4 At the end of the study or WCD device use, the reason for discontinuing will be recorded.

6.4 Long-term Clinical Outcome Assessment

Final survival assessment will be 1 year from WCD start of use, ± 14 additional days.

6.4.1 Sites will be asked to determine survival for all patients enrolled in the study through either routine medical records and appointments, or a phone call to the patient.

6.5 Study Procedures Flowchart (or Table)

Table 1. Study Procedures Table for WCD Pre-study Registry

	Timing of Data Collection (post WCD start)	
Data Collected	Initial Visit (0-30d)	WCD end
Screening (Inclusion criteria, exclusion criteria, consent)	X	
Baseline data (Demographics, Echo, ECG, and clinical characteristics)	X	
Echo data	X	
Medications	X	X
QOL data	X (subset of sites only)	
End of WCD use data (Medical or patient reason for ending use, compliance)		X
Defibrillation data-WCD (Appropriateness, consciousness, effectiveness, clinical status)		X

Table 2. Study Procedures Table for HF Opt study

Data Collected	Enrollment Visit (90d)	120d call	150d call	180d visit	270d visit	360d visit	WCD end
Screening (Inclusion criteria, exclusion criteria, consent)	X						
ECG	X						
Follow-up Echo data	X			X		X	X*

Clinical Status (Medical care utilization, Medications, Symptoms, ICD implantation, SCA	X	X	X	X	X	X	X
QOL data (subset of sites only)	X			X			
End of WCD use data (Medical or patient reason for ending use, compliance)							X
Defibrillation data-ICD or WCD (Appropriateness, consciousness, effectiveness, clinical status)	X	X	X	X	X	X	X
HF diagnostics (Activity, position, heart rate metrics)							X
Long-term survival status						X	X
* If echo performed at end of WCD use, and not at one of the pre-specified timepoints							

6.6 Blinding and Unblinding of Study

NA

7 Study Device Management

The prescription of the study device will be written by the same treating physician who prescribed the device for the first 90 days. Alternatively, another physician at the study site, such as one of the study site investigators, may prescribe the device if the original prescribing physician is no longer available.

7.1 Subject Compliance Monitoring

Patient compliance with the WCD will be assessed through the device records. The WCD compiles compliance data by recording the amount of time the WCD is worn each day. This data, along with the recorded ECG data, is then downloaded to the ZOLL database.

Patient adherence with taking HF medications will be assessed through patient interview at regular intervals. All subjects will be followed regardless of compliance.

Patients who receive an ICD early (prior to reaching GDMT or not otherwise having an indication for an ICD) versus continuing WCD as described by the protocol will not be considered withdrawn from the study, and will continue to be followed.

Patients who refuse an ICD or WCD continuation as described by the protocol (EF ≤ 35%) will not be considered withdrawn from the study, and will continue to be followed..

7.2 Managing WCD Therapy

Since this is an observational, unblinded study, WCD therapy will be handled following normal commercial procedures. However, sites will be notified if a patient receives a shock, and ECG recordings of the event will be sent for the completion of the SCA/Defibrillation event CRF. Evaluation and treatment of patients receiving a shock will be determined by the treating physician.

Treatment events will be initially determined to be appropriate or inappropriate by each site's principal investigator. All shocked events and terminal ECG recordings will be adjudicated by a committee independent of the sponsor. Information regarding the treatment event will be captured in the SCA/Defibrillation event CRF.

7.3 Dispensing, Storage and Return

7.4.1 Dispensing of Study Device

Medical orders and dispensing of the WCD will follow current commercial procedures.

7.4.2 Storage

NA

7.4.3 Return of Study Device

At the completion of the WCD portion of the study, return of the WCD will follow current commercial procedures.

7.4 Device Malfunction or Defect

The WCD System continuously monitors and records critical patient data to help diagnose and treat arrhythmic conditions. Device data will be uploaded at least weekly to a central server located in Pittsburgh, PA. In the event that uploads are not occurring on a routine basis, subjects should call ZOLL Technical Support (800-543-3267) (for Germany call, +49 (0) 2236/878750) for instructions.

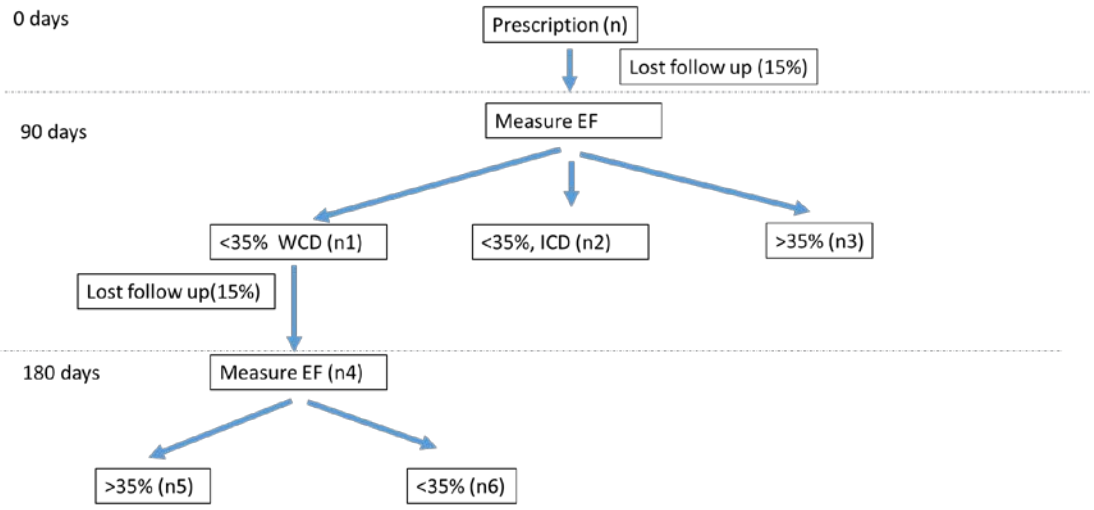
Subjects having questions or difficulty managing their WCD should be referred to the patient manual or instructed to call ZOLL Technical Support (800-543-3267) (for Germany call, +49 (0) 2236/878750).

8 Statistical Plan

8.1 Sample Size and Power Calculation

The total number of WCD prescriptions for the study is estimated to be 868, and assuming ~15% lost follow up, 738 patients will have an EF measurement at day 90. The sample size was calculated using data-based estimates as described below.

8.1.1 Statistical design used for sample size calculation



This dataset will be used evaluate among all patients, if more than 5% of them will experience EF improvement between 90 and 180 days ($n_5/n > 5\%$).

To calculate the number of samples (n), we first calculated n_4, then calculated n based on the following formula:

$$n = \frac{n_4}{P_{followup2}} * \frac{1}{p_{wcd}} * \frac{1}{P_{followup1}}$$

where p_{wcd} is the percentage of patients who will wear WCD beyond 90 days ($n_1/(n_1+n_2+n_3)$), $p_{followup1}$ and $p_{followup2}$ are the percentage of patients with proper follow up from 0 to 90 days and from 90 days to 180 days respectively, both of the them equals to 0.85 (1-0.15=0.85).

To calculate sample size for n_4, we performed superiority test. The statistical hypothesis to be tested is:

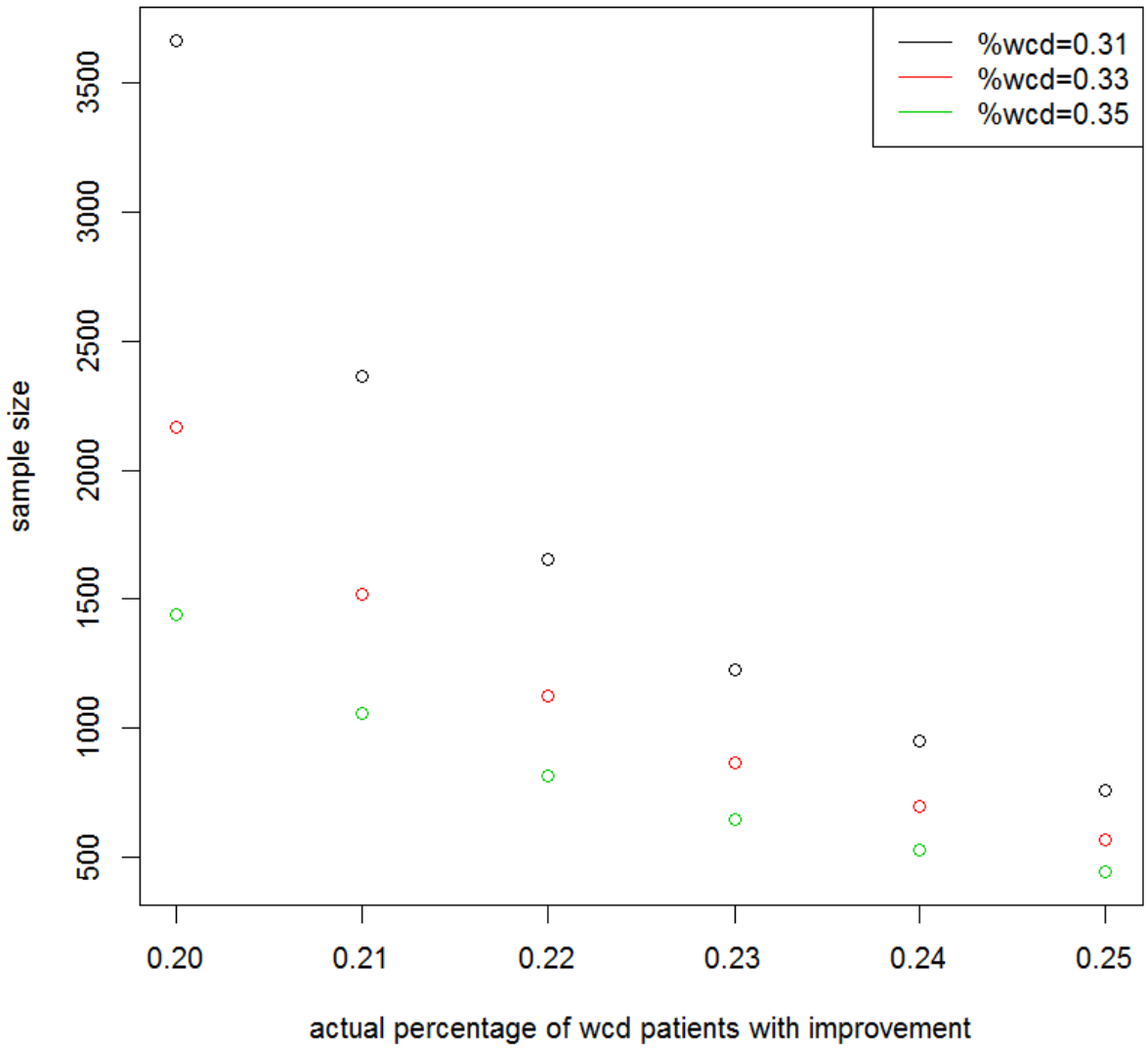
$H0: P \leq P_0 + \delta$ vs $H1: P > P_0 + \delta$

The sample size of superiority test is calculated as the following formula:

$$n_4 = p(1-p)\left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{p - p_0 - \delta}\right)^2$$

where p is the actual proportion of patients who will have EF improvement (n_5/n_4). p_0 is the baseline proportion, and specified as 0.001 (close to 0). δ is the test margin, since the hypothesis is that more than 5% of them will experience EF improvement between 90 and 180 days ($n_5/n > 5\%$), δ depends on p_{wcd} as $\delta = 0.05/P_{wcd}$. We also specify α as 0.05, β as 0.1.

As shown in figure above, sample size (n) depends both on p, the actual proportion of patients who will have EF improvement ($p=n_5/n_4$) and p_{wcd}, the percentage of patients who will wear WCD beyond 90 days ($p_{wcd} = n_1/(n_1+n_2+n_3)$).In this study, we specify α as 0.05, β as 0.1. We predict that about 1/3 patients will have continued WCD wear from 90 to 180 days; and actual proportion of WCD patients at 90 days to have further EF improvement is 23%. In this case, we plan to prescribe WCD to 868 patients (initial registry sample size), in order to have approximately 738 patients eligible for the study at day 90. If mid-study analysis shows continued WCD use to be far out of 1/3, then sample size will be re-adjusted as necessary.



Initial registry sample size vs p, the actual proportion of patients who will have EF improvement between 90 and 180 days and p_{wcd}, the percentage of patients who will wear WCD beyond 90 days.

When the number of patients in WCD group is around ~250, with an estimated rate of shock at 1.5%, the probability of observing two or more events is more than 90%. When the number of patients in WCD group is around 200, with an estimated rate of shock at 1.5%, the probability of observing two or more events is ~80%.

Sample size adjustment (mid-term analysis): As both the dropout ratio prior to the registry and the percentage of patients who will wear the WCD beyond 90 days were higher than predicted, the sample size for the registry and study were recalculated in this protocol revision (version C). The final goal remains to have 200-250 patients in the extended wear WCD group as determined in the preceding paragraph.

8.2 Randomization Scheme

Because WCD's have been shown to be very effective at treating potentially lethal ventricular tachyarrhythmias and are already FDA-approved for use in the study population, randomization will not be done.

8.3 Endpoint Assessment

8.3.1 Primary Endpoint – LVEF recovery and GDMT

Descriptive or summary statistics of serial EF measurements will be used to analyze the rate of recovery of ventricular dysfunction following discharge. For example, the means of EF at 180 days will be compared to the means of EF at baseline and 90 days. The percentage of patients reaching the goal of EF>35% will be compared at 90 days and 180 days. Also, the time taken to reach EF>35% will be calculated for those who improve, and compared between groups (based on baseline characteristics). Individual patient EF measurements over time will be compared to determine whether common patterns arise in certain groups of patients (fast recovery/slow recovery, plateaued recovery/peaked recovery followed by decline).The influence of baseline characteristics on the potential for recovery will be evaluated.

Descriptive statistics will be used to assess the degree GDMT was reached at 90 and 180 days, and how GDMT relates to EF recovery. We will also assess how adherence to the GDMT regimen affects EF recovery and overall clinical improvement.

8.3.2 Secondary Endpoint- Treatments by the WCD or ICD

Treatment events will be initially determined to be appropriate or inappropriate by each site's principal investigator. All shocked events and terminal ECG recordings will be adjudicated by a committee independent of the sponsor.

Effectiveness of the WCD in treating ventricular arrhythmias will be evaluated through descriptive means. Clinical outcomes and device data from any defibrillation or cardiac event will be reviewed for success as defined by appropriate detection and defibrillation, conversion out of the detected ventricular arrhythmia, and consciousness when medically evaluated after treatment.

Descriptive statistics will be used to analyze the incidence of unnecessary shocks from WCD and ICD in this population. Causes of prolonged false detections and lack of response button use in WCD users will be reviewed.

8.3.3 Secondary Endpoint- Incidence of all untreated sustained VT/VF events during WCD use not associated with a shock event (i.e. not within 24 hours of shocked VT/VF event).

Descriptive statistics will be used to analyze the incidence of untreated sustained (≥ 30 seconds) episodes of VT or VF. All possible reasons for a lack of shock will be reviewed, including response button use, rate threshold settings, or ECG artifact. ECG recordings will be adjudicated by a committee independent of the sponsor.

8.3.4 Secondary Endpoint- Incidence of all SCA events

Descriptive statistics will be used to analyze the incidence and etiology of SCA from the beginning of LifeVest use to end of study. “Sudden Cardiac Death” will be defined as an unexpected, non-traumatic, non-self-inflicted fatality in otherwise stable subjects who die within one hour of the onset of the terminal symptoms. Subjects dying more than one hour after a sudden cardiac arrest (SCA) from a ventricular arrhythmia will be designed as non-sudden death due to ventricular arrhythmia. For unwitnessed deaths participants will meet the definition of sudden cardiac 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. Autopsy results may be used when available.

8.3.5 Secondary Endpoint- Incidence and etiology of other WCD recorded arrhythmias, such as asystole and sustained (≥ 30 seconds) supra-ventricular arrhythmias.

Descriptive statistics will be used to analyze the incidence of non-VT/VF events that are recorded by the WCD. Such arrhythmic events will be evaluated for correlation with the other endpoints. ECG recordings will be adjudicated by a committee independent of the sponsor.

8.3.6 Secondary Endpoint- Mortality

Descriptive statistics will be used to analyze the effect of wearable defibrillators on 180-day and 360 day mortality following discharge from HF. Kaplan-Meier curves and survival analysis will be performed both for aggregate mortality and independently for sudden and non-sudden cardiac deaths. Cause of mortality will be adjudicated by a committee independent of the sponsor. The influence of baseline characteristics and EF recovery status on mortality will be evaluated. Comparisons will be made using the Seattle Heart Failure model as a predictive tool of post-discharge mortality.

8.3.7 Safety Endpoint- Complication data from WCD or ICD

Descriptive statistics will be used to analyze the incidence of complications from WCDs and ICDs in this population. This will include inappropriate treatments, as well as any other complications that may lead to hospitalizations or death.

8.4 Statistical Methods

All analyses have been described elsewhere in the protocol.

8.5 Additional Statistical Analysis

NA

8.6 Handling Missing Data

Due to the observational nature of this study and the long term repeated collection of data, missing data is to be expected.

8.6.1 Sources of Missing Data
- 8.6.1.1 Retrospective data (i.e. collection of past medical history).
- 8.6.1.2 Patients who are lost to follow up.
- 8.6.1.3 Patients being un-timely in scheduling their follow-up appointments.

8.6.2 Preventing Missing Data
- 8.6.2.1 Collect only critical data elements that are routinely collected
- 8.6.2.2 All attempts to maintain contact with the patient should be made by study personnel to assure that lost patients are kept to a minimum. This may involve phone calls or patient support groups. Multiple phone numbers/contacts for each patient should be collected. Multiple reminders of upcoming visits should be made.
- 8.6.2.3 Generous windows of time (± 14 days) for follow-up appointments have been employed.
- 8.6.2.4 Routine site monitoring with data verification will occur throughout the study.

8.6.3 Handling missing data
- 8.6.3.1 Loss to follow-up has been anticipated in the sample size calculation.
- 8.6.3.2 Missing data will not be replaced by any algorithm.

8.7 Futility Analysis

NA

9 Health Economic Evaluation

This study will use descriptive statistics to describe information (estimated cost, days, reasons) on any hospitalizations, emergency room visits, observation stays, urgent care visits, other physician office visits, and stays at skilled nursing facilities. This will be related to the outcomes and the type of device therapy that the patient received.

10 Safety and Adverse Device Effects

10.1 Definitions

All device related adverse effects will be recorded during the study. All adverse device effects (ADEs) will classified by the investigator as anticipated or unanticipated. An unanticipated ADE is any adverse effect not identified by nature, severity, or frequency prior to the study.

10.1.1 Common Anticipated Device Effects with Study Device

The following events are commonly reported in patients having HF and therefore should not be reported unless deemed related to WCD wear: dyspnea, fatigue, weakness, edema, chest pain, and a rapid or irregular heartbeat.

Common anticipated device effects that may be caused by WCD use are as follows: skin rash or irritation, sleeplessness due to WCD alarms occurring at night and inappropriate shocks, discomfort from the device.

10.1.2 Unanticipated Adverse Device Effect (UADE)

An unanticipated adverse event is any adverse device effect not identified by nature, severity or frequency prior to the investigation.

If the frequency of inappropriate shocks exceeds 3 per 100 patient months, the inappropriate shocks should be reported as unanticipated adverse device effect.

Any commonly reported adverse events in patients having HF, as mentioned above, should not be reported unless deemed to be related to WCD wear.

10.2 Recording and Reporting of Adverse Device Effects

10.2.1 Investigator Recording and Reporting

The Investigators are responsible for recording and reporting all adverse device effects in the pertinent case report form (CRF). Adverse device effects must be reported to sponsor and reviewing IRBs per local reporting requirements.

The Investigator must next assess the seriousness of the adverse device effect.

Serious injury

Serious adverse device effects include any injury or event that is:

- Fatal or life-threatening, or
- Requiring or prolonging hospitalization, or
- Resulting in permanent impairment of a body function or permanent damage to body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

The Investigator should also assess whether the adverse device effect is anticipated or unanticipated.

At each contact with the subject, the investigator must seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects should be recorded immediately in the source document, and also in the appropriate adverse effect module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse device effects occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period should be recorded and reported promptly.

The minimum initial information to be captured in the subject's source document concerning the adverse device effect includes:

- Study identifier
- Study Center
- Subject number
- Device model and serial number
- A description of the event
- Date of onset
- Investigator assessment of the association between the event and study treatment
- Current status
- Whether study treatment was discontinued
- Whether the event is serious and reason for classification as serious

Serious adverse device effects should be reported to ZOLL immediately.
The ZOLL contact persons for this study are:

In the United States:
Rachel Jackson, Clinical Research Project Manager
1-412-968-3333 ext. 14418 (office phone)
1-412-567-9579 (fax)
rjackson@zoll.com (email)

In Europe:
Horst Esser, Clinical Operations Manager EMEA
+49 (0) 2236/8787 47 (office phone)
hesser@zoll.com (email)

The reviewing ethics committee must also be notified within 10 working days.

All other questions, complaints, or concerns regarding the WCD should be referred to ZOLL's customer support. These are not to be reported as adverse events.

10.3 Protocol Deviations

Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible.

Patients who receive an ICD versus continuing WCD as described by the protocol will not be considered withdrawn from the study or a protocol deviation.

Patients who refuse an ICD or WCD continuation as described by the protocol will not be considered withdrawn from the study or a protocol deviation.

11 Administrative Responsibilities

11.1 Sponsor

ZOLL, the Sponsor, is responsible for study administration as well as providing devices and related materials for the study. The Sponsor will select appropriate investigators, assure collection of investigator agreements, assure IRB approval of the protocol, and monitor informed consent records.

The sponsor may also assist in the screening process by maintaining a current list of eligible patients to be screened by each site (i.e., those patients who are still active WCD users at day 90 ± 14).

The Sponsor will designate appropriately trained and qualified individuals to monitor the investigation. These individuals will verify the adherence to procedures specified in the protocol, and verify maintenance of required subject and data records.

The Sponsor will provide trained and qualified individuals to fit subjects with the WCD and to provide training on the use of the WCD.

11.2 Investigators

The Investigators are responsible for obtaining and maintaining ethics approval of the study protocol. The Investigators are responsible for obtaining patient consent, and maintaining Informed Consent Forms and Case Report Forms for each subject. All forms must be signed by the Investigator or by the Investigator's designee. If the Investigators designate an individual to sign these forms, written notification must be provided to the Sponsor. The Investigators are responsible for maintaining records of study protocol deviations and amendments and all correspondence relating to the study. The Sponsor will provide an Investigator Notebook to serve as a study reference and regulatory binder. At the conclusion of the study, the Investigators will provide a summary report to the Sponsor and the reviewing IRB.

11.3 Data Coordination Center (DCC)

The Data Coordination Center (DCC) has responsibility for clinical data coordination. For this study, ZOLL, the Sponsor, will be the acting DCC.

11.4 Steering Committee

NA, there is no steering committee for this study.

11.5 Data Safety Monitoring Board (DSMB)

The study will not be monitored by an independent Data Safety Monitoring Board (DSMB). ZOLL, the Sponsor, will be the acting DSMB. They will periodically review all aspects of the trial, including inappropriate therapies, to ensure the safety of the participants. The Sponsor is responsible for appointing adjudication committees for significant endpoints including arrhythmia analysis.

12 Data Collection and Management Plan

12.1 Data Collection

This study will collect the following data points:

12.1.1 Patient demographics
12.1.2 Medical history and clinical co-morbidities
12.1.3 Medication list, dosage, and adherence questionnaire
12.1.4 Cardiac symptoms
12.1.5 Device treatment data
12.1.6 ECG recordings
12.1.7 Echo reports
12.1.8 Device discontinuation reason
12.1.9 Mortality questionnaire
12.1.10 WCD data including compliance and HF diagnostic data (activity, position, heart rate metrics)
12.1.11 Medical resource utilization
12.1.12 Quality of Life questionnaire (select sites only)

12.2 Data Handling and Record Keeping

12.2.1 Case Report Forms (CRFs)

Data will be collected at the investigational sites using the electronic data capture (EDC) system Clindex*LIVE* (Fortress Medical Systems, LLC, Hopkins, MN). Electronic Case Report Forms (eCRFs) will be implemented within Clindex*LIVE* by ZOLL's Clinical Data Manager. Data will be entered at the investigational sites by trained staff. Entered data will be reviewed by the site investigator, who will affirm its accuracy and completeness by electronic sign-off. The capability of the Clindex*LIVE* system to implement edit checks during the data entry process (front end edit checks) will be utilized to generate queries automatically at the time of data entry when malformed, out-of-bounds or missing required data are detected. Back end edit checks will be run weekly, to capture data errors and omissions not amenable to front end edit checks, and data that does not pass these checks will be manually queried. Weekly manual review of entered data by ZOLL's Clinical Data Manager and Clinical Scientist will permit identification of any additional data issues, and data queries will be manually generated. All data queries, whether automatically or manually generated, will be communicated to and cleared by investigational site staff via Clindex*LIVE*, which provides a full featured query handling capability. Center staff will either correct or affirm all data that generates queries, which keeps all data processing in the hands of the investigational sites, not ZOLL. ZOLL's Clinical Data Manager and Clinical Scientist will review all cleared queries for appropriateness. A final comprehensive review of all of the data will

occur at the conclusion of the trial. All queries will be resolved and all eCRFs will be electronically signed by appropriate center investigators prior to database lock.

Paper CRFs will be available for recording patient data in the event that the data entry system becomes unavailable because of a technical failure. All paper CRFs will be completed by the same trained personnel who would otherwise use the EDC system. Appropriately completed and signed paper CRFs may become the source data, and will be retained by the individual centers. Once the EDC system again becomes available, the patient data will be transcribed from the paper form into the EDC system by the same person who completed the paper form.

The paper CRFs for this study are documented under 90D0109-CRF.

The QOL CRF (90D0109-QOL) will be collected initially on paper CRFs, and then entered into the EDC system by the sites.

12.2.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

12.2.3 Electronic Data Capture (EDC) System

The Clindex*LIVE* software system was selected for use for this clinical trial because of its full-featured capability, security features, and wide acceptance within the clinical trial industry. ZOLL's Clinical Data Manager, in consultation with ZOLL's Clinical Scientist, will implement the set of eCRFs in Clindex LIVE, and develop a set of test data. User acceptance testing at ZOLL will demonstrate accurate and complete functioning of all data and edit check elements prior to rollout of the EDC system to the investigational sites. The clinical database will be hosted at Fortress Medical Systems, LLC, using redundant on- and off-site resources, throughout the data collection process. Data access (both entry and review) will be controlled by user ID and password restricted user authentication. Only users who have been appropriately trained will be permitted to perform data entry. Once entered by site personnel, data will be reviewed by the site investigator who will have eCRF signature authority. The Clindex*LIVE* system features a fully documented audit trail on all CRF data modified after first pass entry and automatic audit trail on all data changes. Individual report level security allows for a customized report environment for individual users and sites, so that users and sites may access only the data which they have entered into the system. The Clindex*LIVE* system has been independently certified to be 21 CFR Part 11 compliant.

12.3 Data Transmission from Sponsor

NA

12.4 Study Monitoring Plan

Monitoring activities will be conducted according to ZOLL's Monitoring of Clinical Studies Standard Operating Procedure (ZOLL 90D0013) and will be documented.

13 Risks and Benefits

Resuscitation success rates decline approximately 10% per minute of delayed defibrillation (*Larsen MP, Eisenberg MS, Cummins RO, Hallstrom AP*. *Predicting survival from out-of-hospital cardiac arrest: a graphic model*. Ann Emerg Med. *1993*;*22*:*1652–1658*.). The LifeVest is designed to deliver defibrillation within one minute of syncopal VT/VF. Although emergency medical service response times vary by location, the device is expected in general to defibrillate faster than the local emergency medical services response and possibly result in a better resuscitation success rate. Without LifeVest use, the patient is dependent on outpatient emergency medical services for treatment in the event of a sudden cardiac arrest. If the device is not worn, if the device fails to detect an episode of VT/VF, or if having detected the arrhythmia it fails to convert the VT/VF, then the patient would again be dependent on emergency medical services. Prior investigations and current use indicate that the probability of an unnecessary shock episode is less than one per 100 months of patient use [9]. The experience of an unnecessary shock may be painful and startling, but is not likely induce heart damage or arrhythmia. However, there is a small risk that an unnecessary shock will induce a fatal arrhythmia. Non-sustained VT following an inappropriate shock from a wearable cardioverter defibrillator has been observed in about 0.25% of inappropriate shocks (about one in 350 to 400 inappropriate shocks)[22,23].
If standard defibrillation is required on a patient wearing the device, the electrode belt should be unbuckled and the monitor disconnected. If the monitor is not disconnected prior to standard defibrillation, there is a possibility that some of the defibrillation current could be shunted through the electrodes. Although not directly harmful to the patient, such shunting might reduce the effectiveness of the rescue defibrillation. A warning label on the garment instructs emergency medical personnel to disconnect the system before using a standard defibrillator.

14 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

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[22] Szymkiewicz SJ, et al. Incidence and causes of inappropriate defibrillation during wearable defibrillator use. Heart Rhythm. 2009; 6(5, suppl): S74.

[23] Wan C et al. Incidence of inappropriate wearable defibrillator shocks is rare—an evaluation of 15,193 wearable defibrillator patients. Europace. 2011; 13(3):375.

14.1 Subject Consent and Confidentiality

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Document 90D0109-ICF for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

Each subject will receive a unique subject identification number. The subject's name and identity will be known to the local principal investigator and the Sponsor, as necessary for device use and study conduct, but will be kept confidential. Authorized personnel from the IRB and regulatory authorities may have access to original subject records.

At the end of the data collection period, a fully de-identified, HIPAA-compliant dataset will be created using all variables available from the Case Report Forms and device data contained within LifeVest network. This dataset will be used for analysis and publication purposes.

In the event that a subject revokes authorization to collect or use Protected Health Information (PHI), the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

14.2 Subject Financial Responsibility and Stipends

There is no cost to the patient to participate in this research study. The cost of a subject’s ongoing medical care unrelated to the study will remain the responsibility of his/her insurance. The cost of the device will be billed to the patient’s insurance company, or Medicare/Medicaid program, depending on the payer’s approved reimbursement policies. However, if these costs are not reimbursed by the patient’s insurance company or Medicare/Medicaid program, the patient will not be responsible for any insurance co-payments or deductibles related to this study.

15 Publication Plan

15.1 Authorship

The publication committee will consist of the following members:

1. The sponsor’s Vice President of Medical and Clinical Affairs and/ or their representatives, up to three individuals in total.
2. A minimum of 5 physician investigators will be chosen by the sponsor using the following criteria:
   A. Contribution to study design
   B. Contribution to patient enrollment
   C. Contribution to data analysis
   D. Contribution to manuscript preparation

The publication committee will then chose authors based on the above criteria. The publication committee will decide on the publication strategy, including all substudies and other presentations. Physicians on the publication committee can serve as authors. No employees of the sponsor will serve as authors. The authors agree that any proposed publication relating to the research conducted under this protocol will be submitted to the sponsor for review at least forty five (45) days prior to submission for publication. Upon notice by the sponsor during this period that any of sponsor's confidential information is contained in the publication(s) and/or intellectual property considerations apply, the publication may be delayed for an additional period of up to ninety (90) days (for intellectual property considerations) or until all confidential information has been eliminated from the publication(s) and sponsor has approved the publication

15.2 Data ownership

Data resulting from this study are the property of the sponsor, with each site having co-ownership with sponsor of the data generated within their site. The sponsor may make copies of all documents and reports related to the study at sponsor's expense, and all sites will maintain and retain study records for a period of ten (10) years following the termination of the study. The sponsor shall have access to all such records during this period with adequate prior notice and during normal business hours.

16 Intellectual Property and Patents

Copyright and patents related to this research is owned by the sponsor.
Patents related to this research are in place.

17 List of Abbreviations

ADE – Adverse device effect
ATP - Anti-tachycardia pacing
CRF – Case Report Form
CRT – Cardiac Resynchronization Therapy
DCC – Data Coordinating Center
DSMB - Data Safety Monitoring Board
ECHO - Echocardiogram
EC - Ethics Committee
EDC - Electronic data capture
GDMT - Guideline-directed medical therapy
HF - Heart failure
ICD - Implantable cardioverter-defibrillators
IRB - Institutional Review Board
LVEF or EF - Left ventricular ejection fraction
MI – Myocardial infarction
PSR - Patient Service Representative
PHI - Protected Health Information

SCA - Sudden cardiac arrest
SCD - Sudden cardiac death
UADE – Unanticipated adverse device effect
VF – Ventricular Fibrillation
VT– Ventricular Tachycardia
WCD – Wearable Cardioverter Defibrillator

18 Bibliography

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19 Reference Documents

19.1.1 Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
19.1.2 Sample Consent Form (see ZOLL document number 90D0109-ICF)
19.1.3 Study Procedures Flowchart/Table
19.1.4 Study CRFs (see ZOLL document number 90D0109-CRF)
19.1.5 Study Monitoring SOPs (see ZOLL document number 90D0013)
19.1.6 Investigator Brochure (see ZOLL document number 90D00123)
19.1.7 Patient recruitment materials
19.1.8 Quality of Life Questionnaire (see ZOLL document number 90D0109-QOL)